BLA Clinical Review Memorandum

Application Type	BLA
STN	125696
CBER Received Date	12/21/2019
Non-PDUFA Goal Date	1/25/2020
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Kathleen Hise, MD
Review Completion Date / Stamped Date	1/29/2020
Supervisory Concurrence	Sofia Chaudhry, MD Doran Fink, MD, PhD
Applicant	Aimmune
Established Name	Peanut (*Arachis hypogaea*) Allergen Powder
(Proposed) Trade Name	Palforzia
Pharmacologic Class	Allergenic extract
Formulation(s), including Adjuvants, etc.	Powder
Dosage Form(s) and Route(s) of Administration	Capsule/sachet Oral
Dosing Regimen	Once daily
Indication(s) and Intended Population(s)	An oral immunotherapy indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut.
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	Adverse event
AESI	Adverse event of special interest
AIT	Allergen immunotherapy
APAC	Allergenic Products Advisory Committee
BIMO	Bioresearch Monitoring Branch
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
CDER	Center for Drug Evaluation and Research
DBPCFC	Double-blind placebo-controlled food challenge
DRISK	Division of Risk Management
EoE	Eosinophilic esophagitis
ETASU	Elements to ensure safe use
FDA	Food and Drug Administration
GI	Gastrointestinal
IgE	Immunoglobulin E
IDE	Initial dose escalation
OBE	Office of Biostatistics and Epidemiology
OFC	Oral food challenge
OIT	Oral immunotherapy
QoL	Quality of life
REMS	Risk mitigation and evaluation strategy
PI	Prescribing information
PDUFA	Prescription Drug User Fee Act
PeRC	Pediatric Review Committee
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PSP	Pediatric Study Plan
SAE	Serious adverse event

1. EXECUTIVE SUMMARY

A biologics license application (BLA) was submitted by Aimmune Therapeutics to the US Food and Drug Administration (FDA) for peanut (*Arachis hypogaea*) allergen powder. The trade name, Palforzia, will be used in this document. The candidate therapy is initially sourced as shelled, dry roasted peanut (*Arachis hypogaea*) allergen powder and is evaluated for quantities of specific allergenic peanut proteins. The proposed indication is a treatment indicated for the "mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. Initiation of PALFORZIA is approved in patients aged 4 through 17 years with a confirmed diagnosis of peanut allergy."

The BLA includes efficacy and safety data from 7 clinical studies, including two phase 2 studies (ARC001 and ARC002) and 5 phase 3 studies (ARC003, ARC004, ARC007, ARC008, ARC011). ARC003 provided efficacy data, ARC003 and ARC007 provided pooled controlled safety data, and ARC004 and ARC011 provided additional uncontrolled safety data.

ARC003 was a phase 3, randomized, double-blind, placebo-controlled, multicenter study that evaluated the efficacy and safety of Palforzia in 555 subjects 4 to 55 years of age. The majority of participants were 4 through 17 years of age (n = 499). As part of the eligibility criteria, subjects underwent a double-blind placebo-controlled food challenge (DBPCFC) prior to randomization. Subjects were randomized in a 3:1 ratio to receive Palforzia or placebo. The study included 3 dosing phases: an initial dose escalation over 1-2 days under clinical observation, up-dosing every 2 weeks, and maintenance dosing of 300 mg Palforzia daily. The primary efficacy endpoint was the proportion of subjects 4 through 17 years of age in the intent-to-treat (ITT) population who tolerated a dose of at least 600 mg of peanut protein with no more than mild symptoms at the exit DBPCFC at the end of the maintenance period. The ARC003 success criterion was met if the lower bound of the 95% CI for the treatment difference between Palforzia and placebo was greater than 15%.

The ARC003 success criterion was met for the subject population 4 through 17 years of age with a treatment difference (efficacy) estimate of 63.2% (95% CI: 53.0, 73.3). Subjects who did not have an exit DBPCFC were analyzed as non-responders for the primary efficacy endpoint. While discontinuations in the pediatric Palforzia group were elevated in ARC003 (Palforzia 21.4% vs placebo 8.0%), efficacy was demonstrated despite these discontinuations. A sensitivity analysis evaluating a worst-case scenario continued to demonstrate a robust treatment effect.

Palforzia treated subjects in the pediatric safety population reported an increased number of allergic reactions, including systemic allergic reactions, compared to placebo-treated subjects. A total of 9.4% subjects taking Palforzia had a systemic allergic reaction during initial dose escalation and up-dosing compared to 3.8% of placebo subjects. This imbalance was seen during maintenance as well with 8.7% of Palforzia treated patients having a systemic allergic reaction compared to 1.7% of placebo-treated subjects. During the maintenance period, 7.7% of Palforzia treated subjects used epinephrine compared to 3.4% in the placebo group. Twelve subjects treated with Palforzia were diagnosed with eosinophilic esophagitis (EoE) in the entire clinical development program while no subjects in the placebo group of the controlled safety population received a diagnosis of EoE.

The Allergenic Products Advisory Committee (APAC) meeting convened on September 13, 2019 to review and discuss the efficacy and safety data derived from studies conducted with Palforzia and submitted in the BLA. In light of the safety concerns raised by the clinical data, the committee was asked to vote on the safety of Palforzia in the context of the Agency requiring additional post-marketing risk mitigation via a risk evaluation and mitigation strategy (REMS) with elements to ensure safe use (ETASU). The committee voted affirmatively that the available data support the safety (vote: 8 Yes, 1 No, 0 Abstain) and effectiveness (vote: 7 Yes, 2No, 0 Abstain) of Palforzia for the proposed indication.

This reviewer, in consultation with Office of Biostatistics and Epidemiology (OBE) and Division of Risk Management (DRISK) in the Center for Drug Evaluation and Research (CDER) and concurrence from the CBER safety working group, recommends that licensure of Palforzia incorporate additional risk mitigation activities as part of a risk evaluation and mitigation strategy (REMS) with elements to assure

safe use (ETASU) to ensure that the benefits of Palforzia outweigh the risks of systemic allergic reactions due to Palforzia. The REMS with ETASU is discussed in additional detail in the REMS memorandum and is the subject of on-going discussion at the time of this review. The following items in the REMS with ETASU are recommended:

- The healthcare provider will confirm that any patient prescribed Palforzia has a prescription for injectable epinephrine, that the patient has been counseled on the risks of Palforzia and will maintain a peanut avoidant diet.
- Caregivers/patients must receive counseling from the prescriber on the need to have injectable epinephrine available for immediate use while on Palforzia.
- Physician education that initial dose escalation and the first dose of each up-dosing level must be administered in a facility capable of treating systemic allergic reactions.

The Pediatric Research Equity Act (PREA) requires that FDA consider the utility of studying Palforzia in pediatric age groups 0 through 16 years of age. A partial waiver is recommended for children <1 year of age with the rationale based on Section 505B(a)(4)(B)(i) of the Federal Food Drug and Cosmetic Act: necessary studies are impossible or highly impractable because the number of patients diagnosed with peanut allergy is too small. A deferral is recommended for children 1 through < 4 years of age for which one study is on-going. The data for this study is anticipated in the 3rd quarter of 2020. Additionally, this reviewer recommends that the applicant conduct a pregnancy registry study as a postmarketing commitment.

The data submitted by the applicant to the BLA support the approval of Palforzia as a treatment to mitigate allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut in patients aged 4 through 17 years with a confirmed diagnosis of peanut allergy, a population in which no approved therapy exists for preventative treatment. The application is supported by efficacy data from study ARC003: Palforzia recipients demonstrate a strong treatment effect and dose-response to 300mg, 600mg, and 1000mg of peanut protein during a DBPCFC after Palforzia treatment as well as a reduction in the overall severity of allergic symptoms during a DBPCFC when compared to placebo recipients. The increased risks of Palforzia treatment (systemic allergic reactions/anaphylaxis and allergic reactions requiring epinephrine as a rescue medication) necessitate a REMS with ETASU program modeled after study procedures for risk mitigation in the clinical protocols as well as clear information conveyed through the prescribing information (PI) and medication guide. The complex nature of Palforzia administration may limit treatment to those patients/caregivers who fully understand the risks, benefits, and lifestyle/time commitment involved with this therapy; some patients may choose against Palforzia treatment and instead choose only to continue a peanut avoidant diet. However, with proper education and risk mitigation, Palforzia represents a suitable treatment option for peanut-allergic children 4 to 17 years of age.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Review of demographic data for subjects in the main study to support efficacy, ARC003, revealed a balanced distribution between the two study arms with overall percentages of 57.2% male, 79.5% white, and 91.5% not Hispanic or Latino. Most subjects, 78.9%,

resided in the US. The majority of participants were 4 through 11 years of age (59.3%) with a small number of adults participating (10.0%). The population size of non-white subjects was small and a subgroup analysis was not powered to demonstrate efficacy, however, the data trend toward an efficacious treatment effect (Table 13). Additionally, sex and geographic distribution do not appear to affect the treatment effect.

1.2 Patient Experience Data

Patient Experience Data Relevant to this Application

				Section where discussed, if applicable
☐	The patient experience data that was submitted as part of the application include:			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Food allergy arises from a failure of the immune system to generate or maintain tolerance to specific food proteins. IgE-mediated food allergy is a deleterious immune response to food proteins characterized by acute onset of symptoms generally within 2 hours after ingestion of or exposure to the protein [2]. The clinical presentation includes a range of symptoms from oral pruritus to acute urticaria/angioedema which can

progress to more serious sequelae such as anaphylaxis, hypotension, and multiple organ dysfunction syndrome [2].

The most common food allergens are peanut, tree nut, milk, egg, soy, wheat, and shellfish [7]. These foods constitute more than 90% of food allergies in children [8]. Some food allergies (milk, egg, wheat, and soy) have an increased chance of resolving with age whereas others (peanut, tree nut, and shellfish) tend to be persistent over time [9].

Food allergy affects up to 15 million people in the U.S., approximately 6 million of whom are children. Prevalence has been increasing, particularly in children; the National Center for Health Statistics reports that the prevalence increased from 3.4% in 1997-1999 to 5.1% in 2009-2011 in individuals 0 to 17 years of age [10]. Peanut allergy is often diagnosed in childhood when most food allergies develop. The prevalence of peanut allergy in children <5 years of age is estimated to be 0.75-1.3%, and in adults the prevalence is about 0.7% [8]. Only about 20% of children outgrow a peanut allergy [8].

Quality of life (QoL) in food-allergic individuals and their caregivers is often adversely affected due to the fear of accidental ingestion as well as the burden of avoiding allergenic foods which is associated with significant anxiety [11].

Despite peanut avoidance, accidental exposures occur. Two studies estimated that accidental exposures occur at an annual incidence of 12.4% and 14.3% in peanut allergic children [12,13]. The potential consequences of accidental exposure can be serious and life-threatening. About 50% of cases of anaphylaxis reported by emergency departments are due to a food allergen [14]. Fatalities due to anaphylaxis from food allergies are estimated at about 100 per year with most deaths occurring during early adulthood [1].

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

There is no licensed immunotherapy for the treatment of IgE-mediated peanut allergy. Treatment is limited to mitigating the symptoms of allergic reactions after accidental exposure to allergens, either with immediate injection of epinephrine for suspected or confirmed anaphylaxis or with antihistamines for milder symptoms.

2.3 Safety and Efficacy of Pharmacologically Related Products

At present, there is no licensed oral immunotherapy for the treatment of IgE-mediated food allergy.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Not applicable.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The FDA Allergenic Products Advisory Committee (APAC) was convened on January 21, 2016 to obtain advice regarding the design of protocols to evaluate investigational allergenic immunotherapies intended to treat IgE-mediated food allergy. Advice from the

2016 APAC was used to inform the design of the Palforzia development program. The following items summarize the main themes and conclusions from the meeting:

- The committee agreed that a clinically meaningful goal would be to diminish the risk of life-threatening allergy with accidental exposure, acknowledging that data from available studies have not shown induction of full tolerance by oral immunotherapy
- The goal of therapy would be to reduce the risk of life-threatening reactions to accidental exposures instead of allowing patients to add the culprit food to the diet ad lib
- Treatment would focus on increasing the dose of food ingested without a serious allergic reaction after a period of treatment
- The committee agreed that, from a research standpoint, there is no substitute for an oral food challenge (OFC) to determine whether or not a treatment is effective
- A randomized, controlled field study (in subjects practicing allergen avoidance) where the primary endpoint would be a reduction of the rate and/or severity of reactions to accidental food exposure in the treatment arm compared to the control arm, would require large cohorts and long study durations to detect statistically significant differences
- The committee agreed that the safety of using OFCs and oral immunotherapy in food allergy studies can be strengthened by using experts in the field, e.g. those who have experience using immunotherapy and recognizing and treating allergic reactions

The following timeline includes a list of major pre-submission regulatory activity associated with the submission of this BLA:

- April 12, 2013: The applicant submitted an initial Phase 2 study (ARC001) to open IND 15463.
- May 10, 2013: A request for Fast Track status was granted.
- June 15, 2015: A request for Breakthrough Therapy was granted.
- July 20, 2015: A Type B, End of Phase 2 Meeting was held. CBER requested the applicant strengthen the primary endpoint criterion in phase 3 studies for demonstrating the treatment effect between the treatment and placebo groups, ideally with a lower bound of the 95% confidence interval (CI) of about 15% and to extend the maintenance dosing from 3 to 6 months for a total of 12 months in the study.
- January 31, 2017: A teleconference was convened to discuss design elements of phase 3 studies. The applicant agreed to revise the primary efficacy endpoint for study ARC003, to include only pediatric subjects ages 4 to 17 years of age because it was unlikely the number of adults in the study program (N =56) would be adequate to demonstrate effectiveness of the product in the adult population.
- September 24, 2018: A type B, pre-BLA meeting was held. The format and content of including submission of efficacy and safety datasets was agreed upon.

Post submission, a total of 22 amendments were submitted in response to CBER clinical information requests. These amendments satisfactorily addressed all clinical information requests sent during the review period and have been incorporated into this memorandum.

2.6 Other Relevant Background Information

Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The application was adequately organized and integrated to accommodate the conduct of a complete clinical review.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The applicant attested that the studies submitted in support of this application were conducted in compliance with Good Clinical Practices. The Bioresearch Monitoring Branch (BIMO) reviewer noted concerns with Site 009, which participated in studies ARC003 and ARC007. The principal investigator at Site 009 was disqualified in May 2018 and the BIMO reviewer noted data from the inspection of Site 009 "revealed adverse events were not documented as reviewed and evaluated, and there were discrepancies between the source documents and the electronic case report forms for the kit numbers used for two doses."

Clinical Reviewer comment: Efficacy (primary and key secondary endpoints from study ARC003) and pooled safety data study from participants at Site 009, which enrolled a small number of subjects (N=23), were reviewed and compared to datasets excluding data from Site 009 participants. No significant difference in the outcome of the efficacy endpoints or safety analyses were noted. Removal of data derived from Site 009 did not affect any clinical conclusions; therefore, data from Site 009 were not removed from the data presented in the BLA review and USPI.

3.3 Financial Disclosures

Covered clinical study (name and/or number): All studies reviewed in the Clinical Review		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: >100		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 2		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0		

	Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 2		
	Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
	Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) >100			
	Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Clinical Reviewer comment: The number of investigators (N=5) with disclosable financial arrangements enrolled too few subjects to impact data interpretation.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Please see the CMC review for details.

4.2 Assay Validation

Not applicable.

4.3 Nonclinical Pharmacology/Toxicology

Non-clinical studies including pharmacology and toxicology studies were deemed not to be necessary because Palforzia is a food product.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action
The precise mechanisms of action of allergen immunotherapy have not been established.

Clinical Reviewer comment: *Allergen immunotherapy is intended to train the immune system to suppress allergic symptoms. Possible mechanisms include the action of regulatory T cells that promote tolerance to environmental allergens and suppresses allergic inflammation by secreting inhibitory cytokines, a change from a type 2 T helper cell (associated with allergic inflammation) to a type 1 T helper cell cytokine profile, and allergen-specific immunoglobulin G_4 (IgG_4) production which may block the action of IgE-dependent allergic inflammation [15].Because the exact mechanism of action has not*

been established, nor can the above information accurately predict response to immunotherapy, the above language was not included in the prescribing information (PI).

4.4.2 Human Pharmacodynamics (PD)

In ARC003, following treatment with Palforzia, serum peanut-specific IgG4 levels significantly increased from baseline to the exit visit (geometric least squares mean ratio of active/placebo of 1.01 [95% CI: 0.90, 1.12], $p < 0.0001$) and peanut skin prick tests decreased (least squares mean difference of active/placebo of -4.03mm [95% CI: -4.86, 3.21], $p < 0.0001$); the between group least squares mean ratio of active/placebo change in peanut-specific IgE from baseline to study exit was not significant.

Clinical Reviewer comment: The applicant proposes to add the above information to the PI. This reviewer disagreed with the inclusion of the above data in the PI because these data are exploratory and do not reasonably predict response to treatment.

4.4.3 Human Pharmacokinetics (PK)

Not applicable.

4.5 Statistical

A complete statistical review of the clinical studies submitted to the BLA was conducted by Dr. Lei Huang who verified the safety and efficacy data and conclusions submitted to the BLA.

4.6 Pharmacovigilance

A complete review of the pharmacovigilance plan (PVP) was conducted by Drs. Rohan and Day.

During the pre-licensure development program, systemic allergic reactions to Palforzia, including anaphylaxis, were observed to occur during all phases of dosing (initial dose escalation, up-dosing, and maintenance), with highest risk of such reactions associated with the initial dose escalation and up-dosing. In addition to routine pharmacovigilance, to mitigate the risk of systemic allergic reaction including anaphylaxis due to Palforzia and to ensure that the benefits of this product outweigh the risks, the applicant will institute a risk mitigation and evaluation strategy (REMS) with elements to ensure safe use (ETASU). The submission of a REMS proposal by Aimmune was requested following discussions with CBER's Office of Biostatistics and Epidemiology (OBE) and CDER's Division of Risk Management (DRISK) with concurrence from the CBER safety working group. Additionally, the requirement for a REMS was endorsed by the APAC who voted in support of the safety data within the context of requiring additional risk mitigation beyond labeling and routine pharmacovigilance. The six factors considered, as required by Section 505-1(a)(1) of the FD&C Act, as added by FDAAA, were:

1. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
2. The expected benefit of the drug with respect to the disease or condition
3. The seriousness of the disease or condition that is to be treated with the drug
4. Whether the drug is a new molecular entity
5. The expected or actual duration of treatment with the drug

6. The estimated size of the population likely to use the drug

In particular, for Palforzia, the main factors contributing to the decision to require a REMS ETASU were: the imbalance of systemic allergic reactions and epinephrine use as a rescue medication (factor 1) over the duration of treatment (factor 6) which is likely to be life-long as most children do not grow out of IgE-mediated peanut allergy; the seriousness of IgE-mediated peanut allergy which can be fatal (factor 3); and the benefit of treatment as evidenced by the efficacy study ARC003 (factor 2).

The REMS will include the following:

- Documentation that any patient prescribed Palforzia has a valid prescription for injectable epinephrine, has been counseled on the risks of Palforzia, and will maintain a peanut avoidant diet.
- Caregivers/patients must attest to carrying injectable epinephrine while on Palforzia.
- Initial dose escalation and the first dose of each up-dosing level must be administered in a certified facility capable of treating systemic allergic reactions.

Clinical Reviewers Comment: Please see the Pharmacovigilance Plan (PVP) review, CDER DRISK consult and the REMS review memorandum for further details of the REMS program and the supporting documentation of the six statutory factors that were considered during the decision to recommend approval with a REMS. The elements of the REMS program have not been finalized at this time of this review.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The clinical development program for Palforzia included 7 studies (ARC001, ARC002, ARC003, ARC004, ARC007, ARC008, and ARC011) submitted to STN125696. These studies were reviewed under IND15463. Four studies have been completed (ARC001, ARC002, ARC003, and ARC007). The remaining studies are on-going. Two studies, ARC001 and ARC003, were reviewed to support safety and efficacy with ARC003 being the main phase 3 study evaluated for efficacy. ARC007 was a controlled phase 3 study evaluated to support safety along with ARC003. ARC002 was an uncontrolled follow-on study for ARC001 and provided supplemental efficacy and safety data. The remaining studies (ARC004, ARC008, and ARC011) are on-going. Interim safety data from these studies was submitted in the 120 day safety update submitted to the BLA on April 23, 2019.

The efficacy and safety results from ARC003 are presented in Sections 6.1. While study ARC003 enrolled subjects 4-55 years of age, the proposed indication is for use in patients 4-17 years of age. As such, efficacy and safety in subjects 4-17 years of age are the focus of this review. The data in subjects 18-55 years of age are presented and reviewed to provide additional contextual information to assess the benefit/risk of Palforzia, which may be continued in adulthood after initiating treatment at ages 4-17 years. A summary of Phase 3 safety study, ARC007, is presented in Section 6.2. A

summary of Phase 2 study, ARC001 is presented in Section 6.3 as these results were used to inform the design of ARC003.

A summary and discussion of the integrated safety results from ARC003, ARC004, ARC007, and ARC011 studies are presented in Section 8. Data from studies ARC001 and ARC002 are not integrated into the pooled safety datasets due to differences in data collection and ARC008 is not integrated as it contains blinded safety data from a European study, ARC010, which was not submitted for review under IND15463 or to STN125696.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following files served as the basis for the clinical review of STN 125696/0:

- Section 1.2 Cover Letters
- Section 1.3.4 Financial Certification and Disclosures
- Section 1.9 Pediatric Administrative Information
- Section 1.11.3 Clinical Information Amendment
- Section 1.14 Labeling
- Section 1.16 Risk Management Plan
- Section 5 Clinical Study Reports

5.3 Table of Studies/Clinical Trials

Table 1: Summary of Clinical Development

Trial ID *Study Dates (month/year)*	**Trial Design**	**Treatment Arms**	**Study Endpoints**	**Treatment Duration**	**N**	**Study Population** (years of age)	**Countries** (number of sites)
Controlled Studies	--	--	--	--	--	--	--
ARC001 (NCT01987817) *2/14-1/15*	Phase 2, R, DB, PC, MC	300mg Palforzia daily: Placebo (1:1)	Ingestion* of 300mg peanut protein at exit DBPCPC	9 months	56	4-26	US (8)
ARC003 (NCT02635776) *12/15-1/16*	Phase 3, R, DB, PC, MC	300mg Palforzia daily: Placebo (3:1)	Ingestion* of 600mg peanut protein at exit DBPCFC	12 months	555	4-55	NA (51), EU (15)
ARC007 (NCT03126227) *5/17-8/18*	Phase 3, R, DB, PC, MC	300mg Palforzia daily: Placebo (2:1)	Safety	6 months	506	4-17	US (59), CA (5)
Uncontrolled Follow-On Studies	--	--	--	--	--	--	--
ARC002 (NCT02198664) *8/14-1/18*	Phase 2, OL, MC, follow-on for ARC001	300mg Palforzia 2000mg Palforzia	Safety	2.7 years	47	4-26	US (8)
ARC004 (NCT02993107)	Phase 3, OL, follow-	300mg Palforzia daily, QOD,	Safety	3 years	388	4-55	NA (51), EU (13)

Trial ID *Study Dates (month/year)*	**Trial Design**	**Treatment Arms**	**Study Endpoints**	**Treatment Duration**	**N**	**Study Population** (years of age)	**Countries** (number of sites)
Ongoing	on for ARC003	BIW, QW, or QOW					
ARC008 (NCT03292484) *Ongoing*	Phase 3, OL, follow-on for all Palforzia studies	300mg Palforzia daily, QOD, BIW, QW, or QOW	Safety	3 years	360	4-55	US (61), CA (5), EU (18)
ARC011 (NCT03337542) *Ongoing*	Phase 3, OL, follow-on for ARC007	300mg Palforzia daily	Safety	6 months	237	4-17	NA (63)

**Ingestion of peanut protein during DBPCFC with no more than minimal allergic symptoms, R = randomized, DB = double-blind, PC = placebo-controlled, OL = open label, MC = multicenter, US = United States of America, CA=Canada, NA = North America, EU = Europe, DBPCFC = double-blind placebo-controlled food challenge, QOD = every other day, BIW = biweekly, QW = weekly, QOW = every other week*

5.4 Consultations

5.4.1 Advisory Committee Meeting

The Allergenic Products Advisory Committee (APAC) was convened on September 13, 2019, to consider the safety and effectiveness data submitted in support of the requested indication for the age range of 4 through 17 years. The committee voted affirmatively that the available data support the safety (vote: 8 Yes, 1 No, 0 Abstain) and effectiveness (vote: 7 Yes, 2 No, 0 Abstain) of Palforzia treatment for individuals 4 through 17 years of age. In particular, the committee agreed that the available efficacy data are adequate to support the use of Palforzia as a treatment to reduce the incidence and severity of allergic reactions, including anaphylaxis. The committee also agreed the available safety data, in conjunction with additional safeguards (a REMS as summarized in Section 4.6), were adequate to support the use of Palforzia in patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy. Committee members suggested that the REMS should contain additional items including informed consent/assent, documentation that patients and caregivers continue to maintain a peanut-avoidant diet, and guidance on missed doses. One committee member, who voted "No" for both committee questions offered the following concerns:

- Palforzia is intended to prevent allergic reactions upon peanut exposure; however, Palforzia recipients had more allergic reactions requiring epinephrine use compared to placebo recipients.
- Administration of Palforzia is complex because sensitivity to Palforzia can change due to co-factors such as illness and exercise, which changes the risk profile of Palforzia on a day-to-day basis.

Clinical Reviewer comment: Advice garnered from the APAC discussion was taken into consideration during on-going discussions with the applicant, design of the REMS ETASU, PI, and Medication Guide.

5.4.2 External Consults/Collaborations

The clinical review team consulted CBER OBE and CDER DRISK: see Section 4.6 for Pharmacovigilance, Post-Marketing Requirements and REMS ETASU.

5.5 Literature Reviewed

1. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology – European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol. 2012;130(6):1260-74
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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study ARC003

Study Title: Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE)

6.1.1 Objectives (Primary, Secondary)

Primary Objective:

- To demonstrate the efficacy of Palforzia, a pharmaceutical-grade peanut allergen formulation, through reduction in clinical reactivity to limited amounts of peanut allergen in peanut-allergic children aged 4 to 17 years, inclusive

Secondary Objectives:

- To demonstrate the safety of Palforzia measured by the incidence of adverse events, including serious adverse events, in children aged 4 to 17 years, inclusive
- To evaluate the immunologic effects of peanut OIT in children aged 4 to 17 years, inclusive

6.1.2 Design Overview

ARC003 was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial conducted at 66 sites. Of these sites, 51 were in North America and 15 in Europe. The total trial population consisted of 555 subjects 4 to 55 years of age. The population evaluated to support the primary indication, which is restricted to individuals 4 to 17 years of age, consisted of 499 subjects. This latter analysis was pre-specified in protocol amendment 105 (from version 3 to version 4) prior to study unblinding due to low enrollment of adult subjects. Subjects were randomized in a 3:1 ratio to receive treatment or placebo. Randomization was stratified by geographic region (North American and Europe) as well as by age (children from 4 to 17 years of age and adults 18 to 55 years of age).

Prior to enrollment, subjects underwent a screening, double-blind, placebo-controlled oral food challenge (DBPCFC) with up to 100mg peanut protein and placebo to confirm true peanut allergy. Subjects who did not develop dose-limiting symptoms to 100mg of

peanut protein were not eligible for the study. Mild dose-limiting symptoms were determined by a blinded evaluating physician and were identified by evaluating skin, respiratory, gastrointestinal, cardiovascular, and neurologic symptoms. Grading of these reactions was based on the CoFAR grading system for allergic reactions [2].

After randomization, subjects began product dosing with an initial dose escalation of 0.5 to 6mg peanut protein or placebo over 2 days in the clinic. Subsequently, subjects began dosing at 3mg Palforzia or placebo and continued, as tolerated, with up-dosing every 2 weeks (20-40 weeks) until reaching 300mg maintenance treatment (approximately 24-28 weeks). Subjects were continually assessed for allergic symptoms throughout the treatment duration. Allergic symptoms were assessed by the investigator using definitions consistent with the PRACTALL consensus report on DBPCFCs and the CoFAR grading system for allergic reactions [1, 2]. Dose modifications or discontinuation from study treatment could be made based on this assessment but was left to investigator discretion.

The efficacy assessment for the primary endpoint was a DBPCFC performed at the end of the maintenance period for subjects who were able to ingest 300mg daily of Palforzia for 6 months. Single doses of 3, 10, 30, 100, 300, 600, and 1000mg peanut protein or placebo (2043 mg cumulative) were evaluated in the exit DBPCFC. Subjects were considered responders for the primary endpoint if 600mg of peanut protein was ingested with no or only mild symptoms. Dose-limiting symptoms were defined as “any symptoms that, in the investigator’s assessment, indicate poor tolerability of the last challenge dose administered, and preclude safe advancement to the next challenge dose”

6.1.3 Population

Inclusion criteria

- Age 4 through 55 years (inclusive)
- Clinical history of allergy to peanuts or peanut-containing foods
- Serum IgE to peanut ≥ 0.35 kUA/L (determined by a commercial test system, ImmunoCAP, within the past 12 months) and/or a skin prick test to peanut ≥ 3 mm compared with control
- Experience dose-limiting symptoms to a single dose of peanut protein ≤ 100 mg at the screening DBPCFC
- Written informed consent from adult subjects
- Written informed consent from parent/legal guardian for minor subjects
- Written assent from minor subjects as appropriate (above 7 years or applicable age per local regulatory requirements)
- Use of effective birth control by female subjects of childbearing potential
- Not residing at the same address as another subject in this or any peanut OIT study

Exclusion criteria

- History of cardiovascular disease, including uncontrolled or inadequately controlled hypertension
- History of severe or life-threatening episode of anaphylaxis or anaphylactic shock within 60 days of the screening DBPCFC

- History of chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that was, or was at significant risk of becoming, unstable or required a change in chronic therapeutic regimen
- History of eosinophilic esophagitis (EoE), other eosinophilic gastrointestinal (GI) disease, chronic, recurrent, or severe gastroesophageal reflux disease, symptoms of dysphagia (e.g., difficulty swallowing, food getting stuck), or recurrent GI symptoms of undiagnosed etiology
- Current participation in any other interventional study
- Subject was in build-up phase of immunotherapy to another allergen (i.e., has not reached maintenance)
- Severe asthma (2007 National Heart, Lung, and Blood Institute [NHLBI] criteria steps 5 or 6)
- Mild or moderate asthma (2007 NHLBI criteria steps 1-4), if uncontrolled or difficult to control as defined by any of the following:
    - Forced expiratory volume in the first second of expiration (FEV1) < 80% of predicted, or ratio of FEV1 to forced vital capacity (FEV1/FVC) < 75% of predicted, with or without controller medications (only for age ≥6 and able to perform spirometry)
    - Inhaled corticosteroids > 500 mcg daily fluticasone (or equivalent based on NHLBI guidelines)
    - One hospitalization in the past year for asthma
    - Emergency department visit for asthma within 6 months prior to screening
- History of steroid medication use (intravenous [IV], intramuscular [IM], or oral administration) in any of the following:
    - History of daily oral steroid dosing for > 1 month during the past year
    - Burst oral (IM or IV) steroid course in the 3 months prior to randomization
    - > 2 burst oral (IM or IV) steroid courses in the past year of at least 1-week duration
- Inability to discontinue antihistamines for 5 half-lives before the initial day of escalation, skin prick testing, or DBPCFC
- Lack of an available palatable vehicle food to which the subject is not allergic
- Use of any therapeutic antibody (e.g., omalizumab, mepolizumab, reslizumab), any investigational peanut immunotherapy (e.g., oral, sublingual, epicutaneous), or any other immunomodulatory therapy excluding corticosteroids within the past 6 months
- Use of beta blockers (oral), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers
- Pregnant or lactating
- Residing in the same place as another subject in the study
- Participation in another clinical trial within 30 days or 5 half-lives of the investigational product before randomization, whichever was longer
- Developed dose-limiting symptoms to the placebo part of the screening DBPCFC
- History of a mast cell disorder, including mastocytosis, urticaria pigmentosa, and hereditary or idiopathic angioedema
- Allergy to oat
- Hypersensitivity to epinephrine and any of the excipients in the product

Clinical Reviewer comment: The enrollment criteria in ARC003 appropriately define a peanut allergic population for evaluating the efficacy and safety of AR101 by including an entry oral food challenge (OFC). However, in the clinical setting, peanut allergic subjects do not routinely undergo OFCs to determine IgE-mediated peanut hypersensitivity. OFCs are reserved for patients who have clinical and laboratory evidence suggesting the development of tolerance to a food to which they were previously allergic, or, for those who have unclear clinical evidence of a food allergy. In the clinical setting, peanut allergy is generally determined through clinical history, skin prick testing (SPT) to peanut extract and/or peanut-specific serum IgE. In ARC003, the presence of true peanut allergy in the enrolled population was confirmed by DBPCFC to ensure that ARC003 would provide a reliable evaluation of the safety and efficacy of Palforzia. In addition, ARC003 evaluated the ability of Palforzia to decrease allergic symptoms by comparing the amount of peanut protein ingested during the baseline OFC to the end-of-study, or exit, OFC. Please see Section 6.2 for safety study ARC007 for a brief discussion of safety analysis in subjects who did not undergo an entry OFC study to determine study eligibility.

ARC003 excluded subjects who had a reduced ability to tolerate an allergic reaction such as those with a recent history of severe anaphylaxis, those taking beta blockers, or those with uncontrolled asthma. ARC003 also excluded subjects who have a history of eosinophilic gastrointestinal disease including eosinophilic esophagitis (EoE) because EoE is associated with individuals with IgE-mediated food allergy [16], and there is a theoretical concern that oral immunotherapy may unmask this disorder. Labeling negotiations are on-going at the time of this review; however, the proposed label appropriately contraindicates the use of Palforzia with pre-existing EoE and uncontrolled asthma and outlines the risks of use in patients with a reduced ability to tolerate an allergic reaction.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study treatments were either Palforzia or placebo. Subjects were randomized in a 3:1 ratio to Palforzia or placebo, respectively. Palforzia and placebo were matched in appearance and were packaged identically to maintain the treatment blind.

The drug product was encapsulated in hydroxypropyl methyl cellulose (HPMC) or filled in foil-laminate sachets and supplied in color-coded pull-apart capsules at 5 dosage strengths (0.5, 1, 10, 20, and 100 mg) and sachets at 1 dosage strength (300 mg). The corresponding color-matched placebo product consisted of excipients filled in matching capsules or sachets minus the peanut protein.

6.1.5 Directions for Use

Subjects took the first dose of each dose level of the study treatment at the study site and were observed for at least 90 minutes for signs of a reaction. If subjects tolerated the first dose at the study site, subjects were directed to take that same dose level at home for 2 weeks during the up-dosing period and daily during the maintenance period.

Subjects and their caregivers were directed to pull the capsules apart, roll between finger and thumb, followed by a tap to the end of each half of the capsule to ensure full

delivery of contents. The contents of the capsules were then mixed with an age-appropriate vehicle food for ingestion. Study product was not to be added to food heated above room temperature before consumption. If not consumed within 4 hours of mixing into a vehicle, the study product-vehicle food mixture was to be discarded and a new dose mixed prior to consumption. The target interval between doses was at least 8 hours. Subjects were instructed that it is necessary to take the study treatment daily and that no attempt should be made to make up for a missed dose if greater than 6 hours had elapsed since usual time of dosing.

Subjects were instructed not to inhale the powder and take the home dose as part of a meal. In addition, subjects were cautioned against activities likely to increase allergic reactivity such as exercising or taking hot showers/baths within 3 hours after ingestion. Dosing was to be delayed until signs of a hypermetabolic state (e.g., flushing, sweating, rapid breathing, and/or rapid heart rate) resolved. Ingestion was not to occur within 2 hours of bedtime.

6.1.6 Sites and Centers

Study ARC003 was conducted at 66 sites in 10 countries. Fifty-one sites were in North America and 15 in Europe.

6.1.7 Surveillance/Monitoring

The monitoring procedures for study ARC003 are described in Table 2 below.

Table 2: Monitoring and surveillance procedures for study ARC003

Study Period (Time in Days or Weeks)	**Screening**	**Initial Dose Escalation (Days 1-2)**	**Up-Dosing (Every 2 weeks for Weeks 20-40)[1]**	**Maintenance (Every 4 weeks for 24 weeks)**	**Study Exit**
Study Procedures Performed	-ICF -Medical history -Concomitant medications -Physical examination -Labs[2] -Eligibility -Randomization -DBPCFC[3]	-Concomitant medications -Diet history[4] -Physical examination -Assess for AEs, allergic reactions -Study product dosing at site -Study product dispensed for home use	-Concomitant medications -Diet history[4] -Physical examination -Assess for AEs, allergic reactions -Study product dosing at site -Study product dispensed for home use	-Concomitant medications -Diet history[4] -Physical examination -Assess for AEs, allergic reactions -Study product dosing at site -Study product dispensed for home use	-Concomitant medications -Diet history[4] -Physical examination -Labs[2] -Assess for AEs, allergic reactions -DBPCFC[3]

Source: Adapted from BLA125696/0; Clinical Study Report ARC003, Section 9.5.1, Table 3 Study Schedule of Activities
[1]Up-dosing period ranged from 20-40 weeks depending on tolerability of each dose increase
[2]Peanut-specific IgE, IgG4, CBC
[3]Two oral food challenges over a 7-day period with peanut protein and placebo
[4]Food allergen exposure history

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint (North America)
The primary endpoint was the proportion of subjects aged 4 to 17 years who tolerated a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC. Subjects who tolerated 600mg were considered responders for the primary efficacy endpoint. The primary efficacy estimate was calculated as the treatment difference in the response rate relative to placebo (treatment with Palforzia – placebo). The pre-specified success criterion for efficacy was met if the lower bound of the corresponding 95% CI was greater than 15%.

Clinical Reviewer comment: The pre-specified criterion for success was agreed upon between CBER and the applicant at the End of Phase 2 (EOP2) meeting. The lower bound of 15% (of the 95% CI) was determined to represent a clinically meaningful benefit. The efficacy results from phase 2 study ARC001 were used to inform this success criterion. The response rate in the Palforzia arm of the ARC001 study was 79% (95% CI of 60% to 92%) and 62% (95% CI of 42% to 79%) for endpoints based on tolerating 300 mg and 600 mg respectively at the exit DBPCFC. A higher lower bound was chosen to ensure that clinically relevant treatment benefit was demonstrated.

The primary efficacy endpoint was amended prior to unblinding of the trial. The age of subjects evaluated for the primary endpoint was amended from 4 to 55 years of age to 4 to 17 years of age because the study enrolled a small number of adult subjects. This protocol revision was deemed to be reasonable as the limited number of enrolled adults would not be sufficient to determine statistically significant efficacy nor would it provide a reasonable evaluation of safety in adult subjects. Importantly, this change was made prior to unblinding of the study data.

Key Secondary Efficacy Endpoints

1. The proportion of subjects aged 4 to 17 years who tolerated a single highest dose of at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC
2. The proportion of subjects aged 4 to 17 years who tolerated a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC
3. The maximum severity of symptoms in subjects aged 4 to 17 years occurring at any challenge dose of peanut protein during the Exit DBPCFC
4. The proportion of subjects aged 18 to 55 years who tolerated a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC

Other Secondary Endpoints

5. Maximum dose achieved with no or mild symptoms at Exit DBPCFC in subjects aged 4 to 17 years
6. Change from baseline in maximum tolerated dose of peanut protein at DBPCFC in subjects aged 4 to 17 years
7. Use of epinephrine as a rescue medication at Exit DBPCFC and comparison to its use at Screening DBPCFC in subjects aged 4 to 17 years

8. Changes in peanut-specific serum IgE and IgG4 levels in subjects aged 4 to 17 years
9. Changes in peanut skin prick test (SPT) mean wheal diameters in subjects aged 4 to 17 years
10. Quality of life assessments using the food allergy related quality of life questionnaire (FAQLQ) and the food allergy independent measure (FAIM) questionnaire in subjects aged 4 to 17 years

Secondary Safety Endpoints

1. The safety of peanut OIT based on adverse events (AEs) including serious adverse events (SAEs) in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
2. Use of epinephrine as a rescue medication during OIT (Initial Escalation, Up-dosing, and Maintenance Periods) in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
3. Frequency of anaphylaxis during OIT (Initial Escalation, Up-dosing, and Maintenance Periods) in in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
4. Frequency of allergic reaction (hypersensitivity) AEs occurring during the Up-dosing versus the Maintenance Period, normalized for duration of treatment in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
5. Frequency of accidental ingestions of peanut and other allergenic foods in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
6. Severity of adverse events associated with accidental ingestions of peanut and other allergenic foods in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
7. Frequency of premature discontinuation of dosing due to AEs; and frequency of premature discontinuation of dosing due to chronic/recurrent gastrointestinal (GI) AEs in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
8. Assessment of asthma control using the Asthma Control Test questionnaire in subjects with asthma in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive

Exploratory Endpoints

1. The primary endpoints identified above will be repeated in the following 3 age groups: 4 to 11 years, 12 to 17 years, and 4 to 55 years, inclusive
2. The first 3 secondary endpoints and all other secondary endpoints identified above will be repeated in the following 4 age groups: 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
3. Treatment satisfaction assessment using the Treatment Satisfaction Questionnaire for Medication (TSQM-9), an exit questionnaire and palatability questions
4. Optional (b) (4) obtained longitudinally from peanut-allergic participants undergoing OIT in ARC003 (North America sites only)

6.1.9 Statistical Considerations & Statistical Analysis Plan

The target sample size of approximately 500 subjects for ARC003 was selected to provide sufficient power to demonstrate a Palforzia responder rate that is higher than placebo by a least a 15% margin to satisfy the pre-specified success criterion for this trial. This sample size was calculated based on an assumed responder rate of 20% and 50% for the placebo and Palforzia treatment groups respectively. These assumptions were supported by the responder rates seen in the phase 2 study ARC001 which included a 0 to 19% point estimate for the placebo responder rates to 300 and 600 mg peanut protein during the exit DBPCFC, respectively, and a 62 to 79% response rate for the Palforzia treatment arm. The 50% Palforzia response rate was chosen to account for estimates as low as 42% to 60% based on the lower bound of the 95% confidence interval from this phase 2 study.

Unless otherwise stated in the review, all statistical tests were conducted at $\alpha = 0.05$ (2-sided) level. The primary and key secondary endpoints were tested in a stepwise procedure, where statistical conclusions were made on the primary and first 4 key secondary efficacy endpoints (see Section 6.1.8) only if statistical significance was demonstrated in the primary efficacy endpoint.

Please see the statistical review for a detailed description of the statistical analysis plan for ARC003.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The definitions of the analysis populations are presented below.

Intent-to-Treat (ITT)
This population served as the primary analysis population for the evaluation of efficacy data. It consisted of all randomized subjects who received at least one dose of randomized study treatment.

Completer Population
The Completer population included all subjects in the ITT population who completed treatment and have an evaluable Exit DBPCFC. An evaluable Exit DBPCFC is defined as completion of at least the peanut part of the food challenge. Sensitivity analyses, supportive analyses of the primary endpoint, and key secondary endpoints, and other secondary endpoints using the Completer population are presented and analyzed.

Per Protocol (PP) Population
The Per Protocol (PP) population is a subset of the Completer population and consisted of subjects with no major protocol deviations.

Safety Population
The Safety population consists of all subjects who received at least one dose of randomized study treatment. The Safety population is used for summaries of safety parameters. The safety population included all subjects according to the actual treatment received not the assigned treatment group.

6.1.10.1.1 Demographics
The demographics of pediatric study subjects participating in ARC003 are shown below in Table 3.

Table 3: Demographic Characteristics of Randomized Subjects Pediatric Subjects 4 through 17 Years of Age (ITT population): Study ARC003

	Palforzia N(%)	**Placebo N(%)**	**Total N(%)**
Number of subjects	372	124	496
Gender:	--	--	--
Male	208 (55.9)	76 (61.3)	284 (57.3)
Female	164 (44.1)	48 (38.7)	212 (42.7)
Age (years):	--	--	--
4 to 11	238 (64.0)	89 (71.8)	327 (65.9)
12 to 17	134 (36.0)	35 (28.2)	169 (34.1)
Race	--	--	--
White	292 (78.5)	97 (78.2)	389 (78.4)
Black or African American	6 (1.6)	3 (2.4)	9 (1.8)
Asian	41 (11.0)	8 (6.5)	49 (9.9)
American Indian or Alaska Native	1 (0.3)	0	1 (0.2)
Native Hawaiian or Other Pacific Islander	31 (8.3)	16 (12.9)	47 (9.5)
Other	292 (78.5)	97 (78.2)	389 (78.4)
Ethnicity	--	--	--
Hispanic or Latino	29 (7.8)	15 (12.1)	44 (8.9)
Not Hispanic or Latino	343 (92.2)	109 (87.9)	452 (91.1)
Geographic Region	--	--	--
North America	302 (81.2)	100 (80.6)	402 (81.0)
Europe	70 (18.8)	24 (19.4)	94 (19.0)

Source: Adapted from 125696/0: Clinical Study Report ARC003, Table 14.1.3.10
N= number of subjects

*Clinical Reviewer comment: The ARC003 study population is primarily Caucasian/White (79.5%). In addition, male subjects comprise a slight majority of the enrolled population (56.4% male vs 43.6% female). It has been noted that male children are at higher risk for food allergy, in particular peanut allergy [4]; however, a CDC survey reports male and female children 5 to 17 years of age have similar rates of food allergy as do non-Hispanic White and Black children in the US [5]. Based on the findings from this report, the enrolled population doesn't fully reflect the patient population likely to use the Palforzia in practice. While the data may be limited, the relevance of this difference is questionable because the clinical diagnosis of IgE-mediated food allergy is relatively straightforward and is unlikely to be affected by sex, race or ethnicity. Importantly, subgroup analyses by sex and ethnicity do not reveal any demographic-related treatment differences. Unfortunately, the low enrollment of non-White subjects limits the interpretation of any treatment differences in the Black population (*Table 13*).*

The study population is predominantly North American and, as outlined in Table 13, no regional differences in efficacy are seen. As such, the data from ARC003 can be generalized to inform the licensure of Palforzia in for use in the US.

A similar breakdown was seen in adults 18 through 55 years of age, though more adult participants were located in Europe (60% in North America and 40% in Europe) compared to pediatric participants. The demographics were balanced across treatment groups in the adult population. The applicant seeks an indication in persons 4 through 17 years of age although the study includes small numbers of persons outside this age range. Since these numbers are small, data from this study are insufficient to establish safety and effectiveness in persons <4 or >17 years of age.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

In subjects 4 to 17 years of age, the median time since peanut allergy diagnosis was 87 months. Of these subjects, 138 (27.8%) had no history of systemic allergic reactions to peanut, 209 (42.1%) had 1, 83 (16.7%) had 2, 36 (7.3%) had 3, and 30 (6.0%) had >3 reactions. Most subjects had a food allergy other than peanut (65.5%). Other common atopic conditions included allergic rhinitis (71.8%), asthma (52.8%), and atopic dermatitis (62.1%). These conditions were balanced across treatment groups. All subjects reacted at 100mg or less of peanut protein during entry DBPCFC and the proportion of subjects who reacted at a particular dose (subjects who reacted at 1, 3, 10, 30, or 100mg peanut protein) were balanced across treatment groups.

In subjects 18 to 55 years of age the median time since peanut allergy diagnosis was 219 months. Of these subjects, 6 (10.9%) had no reported history of systemic allergic reactions to peanut, 12 (21.8%) had 1, 13 (23.6%) had 2, 10 (18.2%) had 3, and 14 (25.5%) had >3 reactions. Most subjects had a food allergy other than peanut (58.5%). Other common atopic conditions included allergic rhinitis (72.7%), asthma (65.5%), and atopic dermatitis (58.2%). These conditions were balanced across treatment groups. All subjects reacted at 100mg or less of peanut protein during entry DBPCFC and the proportion of subjects who reacted at a particular dose (subjects who reacted at 1,3,10,30, or 100mg peanut protein) were generally balanced across treatment groups, though the numbers of adult subjects were small.

6.1.10.1.3 Subject Disposition
The table below outlines subject disposition in study ARC003.

Table 4: Study ARC003: Subject Disposition by Age Group

Disposition	Palforzia N (%)	Placebo N (%)	Total N (%)
Study Disposition (4 to 17 years of age):	--	--	--
Randomized	374	125	499
Treated	372	124	496
ITT[1]	372 (99.5)	124 (99.2)	496 (99.4)
PP	289 (77.3)	113(90.4)	402 (80.6)
Completer	296 (79.1)	116 (92.8)	412 (82.6)

Disposition	Palforzia N (%)	Placebo N (%)	Total N (%)
Safety	372 (99.5)	124 (99.2)	496 (99.4)
Discontinued[2]	80 (21.4)	10 (8.0)	90 (18.0)
Adverse event	34 (9.1)	2 (1.6)	36 (7.2)
Withdrew consent	31 (8.3)	6 (4.8)	37 (7.4)
Initial dose escalation failure	4 (1.1)	1 (0.8)	5 (1.0)
Up-dosing failure	4 (1.1)	0	4 (0.8)
Maintenance dose failure	1 (0.3)	0	1 (0.2)
Investigator decision	1 (0.3)	0	1 (0.2)
Other[3]	5 (1.3)	1 (0.8)	6 (1.2)
Study Disposition (18 to 55 years of age):	--	--	--
Randomized	42	14	56
Treated	41	14	55
ITT[5]	41 (97.6)	14 (100.0)	55 (98.2)
PP	20 (47.6)	13 (92.9)	33 (58.9)
Completer	20 (47.6)	13 (92.9)	33 (58.9
Safety	41 (97.6)	14 (100.0)	55 (98.2)
Discontinued[2]	22 (52.4)	1 (7.1)	23 (41.0)
Adverse event	6 (14.3)	0	6 (10.7)
Withdrew consent	10 (23.8)	1 (7.1)	11 (19.6)
Initial dose escalation failure	0	0	0
Up-dosing failure	2 (4.8)	0	2 (3.6)
Maintenance dose failure	0	0	0
Investigator decision	0	0	0
Other[4]	4 (9.5)	0	4 (7.1)

Adapted from125696/0: Clinical Study Report ARC003, Table14, Figure 2 & 3
[1]Two subjects did not receive Palforzia; 1 withdrew consent, 1 was a randomization error. One subject in the placebo group withdrew consent
[2]Percentage calculated from number of subjects randomized into each arm
[3]In the Palforzia group the reasons listed for "other" are: non-compliance (2), relocation (1), schedule conflict (1), and randomized in error (1). In the placebo group one subject discontinued due to relocation
[4]In the Palforzia group the reasons listed for "other" are: lost to follow-up (2), no longer met eligibility criteria (1), unable to tolerate smell/taste of study product (1)
[5] One subject no longer met eligibility criteria

<u>Clinical Reviewer comment</u>: In pediatric subjects 4 to 17 years of age, more Palforzia treated subjects discontinued compared to placebo treated subjects (21.4% vs. 8.0%, respectively). The most common reasons for discontinuation were adverse events and withdraw of consent. This trend was similar in adult subjects, though a greater proportion of adult subjects discontinued (52.4% vs. 7.1%; data not shown). Treatment with Palforzia resulted in a substantial proportion of discontinuations due to adverse events and withdraw of consent. It is unclear if, had these subjects chosen to continue in study ARC003, a higher rate of adverse reactions would have been reported in the treatment arm. It is notable that adult subjects, who are more autonomous than pediatric subjects, chose to withdraw at a higher rate than pediatric subjects. As many of the tolerability concerns are self-evident, patients/caregivers who do not tolerate Palforzia are likely to choose to discontinue immunotherapy early in the treatment course at rates similar to, if not higher, than what was seen in ARC003. Thus, the postmarketing rates of adverse reactions are anticipated to be similar to those seen in ARC003.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

The primary efficacy assessment was the proportion of subjects aged 4 to 17 years in the ITT population who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC. Subjects who tolerated 600mg were considered responders for the primary efficacy endpoint. The primary efficacy endpoint was calculated as the treatment difference in the responder rate relative to placebo (treatment with Palforzia – placebo). The pre-specified criterion for efficacy was demonstrated if the lower bound of the corresponding 95% CI is greater than 15%.

Table 5: Efficacy Analysis of the Primary Endpoint in the Intent-To-Treat (ITT) population in Subjects 4 to 17 Years of Age: Study ARC003

Treatment	N	% Responders (95% CI)	% Treatment difference (Palforzia-placebo) (95% CI)	P-value
Palforzia	372	67.2 (62.3, 71.8)	63.2% (53.0, 73.3)	<0.0001
Placebo	124	4.0% (1.7, 9.1)	--	--

Adapted from 125696/0 Clinical Study Report ARC003 Table 23
CI=confidence interval
N=number

Clinical Reviewer comment: The primary efficacy endpoint result met the pre-specified criterion for success supporting the effectiveness of Palforzia. As discussed earlier, the success criterion for this trial were previously agreed upon between the applicant and the Agency. The criterion was chosen to reflect a clinically meaningful improvement and Palforzia exceeded this threshold in subjects 4-17 years of age. When evaluating the primary endpoint in the completer population (which contained only subjects who underwent the exit DBPCFC), 80.1% (95% CI: 69.7%, 90.6%) were able to ingest 600mg of peanut protein with no more than mild symptoms, which further supports the primary endpoint result.

Sensitivity Analyses of the Primary Efficacy Endpoint

Sensitivity analyses of the primary efficacy endpoint conducted by the sponsor to evaluate the impact of missing data included: using a worst-case scenario for missing data imputation, a tipping point analysis, and the exclusion of subjects with indeterminate exit DBPCFC.

For the worst-case imputation, placebo-treated subjects with missing data for the exit DBPCFC were considered as responders and Palforzia-treated subjects with missing data for the exit DBPCFC were considered as non-responders. Subjects who had indeterminate DBPCFCs were identified as those without an exit DBPCFC and those who were unable to tolerate at least 1000mg during the placebo portion of the DBPCFC. The analyses for worst-case imputation and exclusion of subjects with an indeterminate exit DBPCFC are presented in tables below.

A tipping point analysis was performed to identify the point at which the number of placebo-treated subjects with missing data imputed as responders rendered the

significant treatment effect difference nonsignificant. Since the tipping point analysis started with the worst-case imputation which met the pre-specified success criterion, no tipping point was found.

Table 6: Selected Sensitivity analyses of the Primary Endpoint in the Intent-To-Treat (ITT) population in Subjects 4 to 17 Years of Age: Study ARC003

Treatment	**N**	**% Responders (95% CI)**	**% Treatment difference (Palforzia-placebo) (95% CI)**	**P-value**
Worst-case imputation analysis	--	--	--	--
Palforzia	372	67.2 (62.3, 71.8)	56.7 (46.6, 66.9)	<0.0001
Placebo	124	10.5 (6.2, 17.1)	--	--
Exclusion analysis[1]	--	--	--	--
Palforzia	372	66.6 (61.5, 71.3)	62.3 (81.8, 72.7)	<0.0001
Placebo	124	4.3 (1.9, 9.7)	--	--

Adapted from 125696/0 Clinical Study Report ARC003 Table 25
[1] Exclusion of subjects with indeterminate exit DBPCFC

Clinical Reviewer comment: The sensitivity analyses to account for missing data are particularly important for this development program given the imbalance between treatment and placebo groups due to study discontinuation. All three sensitivity analyses support the robustness of the treatment effect demonstrated by Palforzia in this study. In particular, the worst-case imputation is compelling given the conservative nature of this analysis.

6.1.11.2 Analyses of Secondary Endpoints

Key secondary analyses include:

1. The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC
2. The proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC
3. The maximum severity of symptoms in subjects aged 4 to 17 years occurring at any challenge dose of peanut protein during the Exit DBPCFC
4. The proportion of subjects aged 18 to 55 years who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC

The key secondary endpoints were tested in a stepwise procedure, where statistical conclusions were made on the primary and first 4 secondary efficacy endpoints (see sections 6.1.8 and 6.1.9). Below are the results of the key secondary endpoints in tabular format.

Table 7: Secondary Efficacy Analysis of the Proportion of Subjects who Ingested 300mg of Peanut Protein at the Exit DBPCFC in the ITT Population 4 to 17 Years of Age: Study ARC003

Treatment	N	% Responders (95% CI)	% Treatment difference (Palforzia-placebo) (95% CI)	P-value
Palforzia	372	76.6 (72.1, 80.6)	68.5 (58.6, 78.5)	<0.0001
Placebo	124	8.1(4.4, 14.2)	--	--

Adapted from 125696/0 Clinical Study Report ARC003 Table 29

Table 8: Secondary Efficacy Analysis of the Proportion of Subjects who Ingested 1000mg of Peanut Protein at the Exit DBPCFC in the ITT Population 4 to 17 Years of Age: Study ARC003

Treatment	N	% Responders (95% CI)	% Treatment difference (Palforzia-placebo) (95% CI)	P-value
Palforzia	372	50.3 (45.2, 55.3)	47.8 (38.0, 57.7)	< 0.0001
Placebo	124	2.4% (0.8, 6.9)	--	--

Adapted from 125696/0 Clinical Study Report ARC003 Table 29

Clinical Reviewer comment: The data presented in Table 7 *and* Table 8 *(responders to both 300mg and 1000mg during the exit DBPCFC) demonstrate a consistent response in Palforzia treated subjects. The responder rate tends to decrease with increasing amounts of ingested peanut protein in both Palforzia and placebo treated subjects. It is notable that of the subjects who were able to ingest 300 mg of peanut protein with no more than mild symptoms (Table 8), about 23% of these subjects were considered non-responders in the ITT analysis. This finding is interesting because the maintenance treatment dose is 300 mg of peanut protein and most subjects should be able to demonstrate tolerability of this dose during the Exit DBPCFC. This suggests that subjects' ability to ingest a discrete amount of peanut protein with no more than mild symptoms varies day to day. Further studies will be essential to elucidate the co-factors that contribute to this variance. Not surprisingly, the number of responders decreased as the peanut protein challenge dose was further increased to 600mg and 1000mg; although it is notable that approximately 50% of Palforzia subjects were able to ingest 1000 mg with no to mild symptoms on exit challenge.*

Table 9: Secondary Efficacy Analysis of the Maximum Severity of Symptoms at any Challenge Dose of Peanut Protein during the Exit DBPCFC in the ITT Population 4 to 17 Years of Age: Study ARC003

Treatment	Total N	None	Mild	Moderate	Severe or higher[1]
Palforzia N (% of total)	372	140 (37.6)	119 (32.0)	94 (25.3)	19 (5.1)
Placebo N (% of total)	124	3 (2.4)	35 (28.2)	73 (58.9)	13 (10.5)

Adapted from 125696/0 Clinical Study Report ARC003 Table 29

[1] Includes severe symptoms, life-threatening or fatal reactions. No subjects had symptoms considered life-threatening or fatal

Clinical Reviewer comment: Compared to placebo, the Palforzia group experienced less severe symptoms at any challenge dose, suggesting that treatment with Palforzia decreased the severity of IgE-mediated allergic responses upon ingestion of up to 1000mg peanut protein.

Table 10: Secondary Efficacy Analysis of the Proportion of Subjects who ingested 600mg of peanut protein at the Exit DBPCFC in the ITT Population 18 to 55 Years of Age: Study ARC003

Treatment	N	% Responders (95% CI)	% Treatment difference (Palforzia-placebo) (95% CI)	P-value
Palforzia	41	41.5 (27.8, 56.6)	27.2 (-1.7, 56.0)	0.0648
Placebo	14	14.3 (4.0, 39.9)	--	--

Adapted from 125696/0 Clinical Study Report ARC003 Table 29

Clinical Reviewer comment: This subgroup analysis in the adult population was not statistically significant. The small number of adult participants precluded an accurate assessment of the efficacy in adults. However, those results trended towards a positive Palforzia treatment effect. Additional clinical evaluation in an adult population is necessary to support licensure for the initiation of treatment in this patient population. However, data in the adult completer population (evaluation of adult subjects who had an evaluable Exit DBPCFC: 69.6% (95% CI: 35.1, 100.0)) provide sufficient reassurance to support the continued treatment of patients as they age beyond the approved age range for treatment initiation.

6.1.11.3 Subpopulation Analyses

Table 11: Subpopulation Efficacy Analysis of the Proportion of Subjects who ingested 600mg of peanut protein at the Exit DBPCFC in the ITT Population 4 to 11 Years of Age: Study ARC003

Treatment	N	% Responders (95% CI)	% Treatment difference (Palforzia-placebo) (95% CI)	P-value
Palforzia	238	70.6 (64.5, 76.0)	66.1 (53.9, 78.3)	< 0.0001
Placebo	89	4.5 (1.8, 11.0)	--	--

Adapted from 125696/0 Clinical Study Report ARC003 Table 24

Table 12: Subpopulation Efficacy Analysis of the Proportion of Subjects who ingested 600mg of peanut protein at the Exit DBPCFC in the ITT Population 12 to 17 Years of Age: Study ARC003

Treatment	N	% Responders (95% CI)	% Treatment difference (Palforzia-placebo) (95% CI)	P-value
Palforzia	134	61.2 (52.7, 69.0)	58.3 (39.7, 76.9)	< 0.0001

Placebo	35	2.9 (0.5, 14.5)	--	--

Adapted from 125696/0 Clinical Study Report ARC003 Table 24

Clinical Reviewer comment: Analysis of the primary efficacy endpoint in subpopulations of young children (4 to 11 years of age) and adolescents (12 to 17 years of age) demonstrate a consistent response across both groups in Palforzia treated subjects. It appears young children may have an increased response to treatment (i.e. greater ability to ingest 600gm peanut protein with no more than mild symptoms during the exit DBPCFC); however, this study was not powered to show a difference between these two age groups. This age-related trend follows through to the adult population (see Table 10 *above).*

Table 13: Subpopulation Efficacy Analysis of the Proportion of Subjects who ingested 600mg of peanut protein at the Exit DBPCFC in the ITT Population 4 to 17 Years of Age by Geographic region, Sex, Race, Ethnicity, Peanut-specific Serum IgE, and Asthma History: Study ARC003

Treatment	**N**	**% Responders (95% CI)**	**% Treatment difference (Palforzia-placebo) (95% CI)**	**P-value**
North America	--	--	--	--
Palforzia	302	65.6 (60.0, 70.7)	62.6 (51.3, 73.9)	< 0.0001
Placebo	100	3.0 (1.0, 8.5)	--	--
Europe	--	--	--	--
Palforzia	70	74.3 (63.0, 83.1)	66.0 (43.0, 88.9)	<0.0001
Placebo	24	8.3 (2.3, 25.8)	--	--
Male	--	--	--	--
Palforzia	208	62.5 (55.8,68.8)	63.2 (53.0, 73.3)	< 0.0001
Placebo	76	6.6 (2.8, 14.5)	--	--
Female	--	--	--	--
Palforzia	164	73.2 (65.9, 79.4)	73.2 (57.2, 89.1)	< 0.0001
Placebo	48	0.0 (0.0, 7.4)	--	--
IgE < 100 kUA/L	--	--	--	--
Palforzia	212	80.2 (74.3, 85.0)	65.7 (52.7, 78.7)	<0.0001
Placebo	69	14.5 (8.1, 24.7)	--	--
IgE ≥ 100 kUA/L	--	--	--	--
Palforzia	160	65.6 (58.0, 72.5)	65.6 (50.2, 81.0)	<0.0001
Placebo	54	0 (0.0, 6.6)	--	--
History of Asthma	--	--	--	--
Palforzia	197	61.4 (54.5, 67.9)	56.8 (42.8, 70.8)	<0.0001
Placebo	65	4.6 (1.6, 12.7)	---	

Treatment	N	% Responders (95% CI)	% Treatment difference (Palforzia-placebo) (95% CI)	P-value
Race[1]	--	--	--	--
White	--	--	--	--
Palforzia	292	66.1% (60.5, 71.3)	63.0% (51.5, 74.5)	< 0.0001
Placebo	97	3.1% (1.1, 8.7)	--	--
Black or African American	--	--	--	--
Palforzia	6	66.7 (30.0, 90.3)	66.7 (-2.2, 100.0)	0.0578
Placebo	3	0.0 (0.0, 56.1)	--	--
Asian	--	--	--	--
Palforzia	41	73.2 (58.1, 84.3)	73.2 (36.3, 100.0)	0.0001
Placebo	8	0.0 (0.0, 32.4)	--	--
Other	--	--	--	--
Palforzia	31	71.0 (53.4, 83.9)	58.5 (28.3, 88.6)	0.0001
Placebo	16	12.5 (3.5, 36.0)	--	--
Not Hispanic or Latino	--	--	--	--
	--	--	--	--
Palforzia	343	65.5 (47.3, 80.1)	58.9 (27.8, 89.9)	0.0002
Placebo	109	6.7 (1.2, 29.8)	--	--
Hispanic or Latino	--	--	--	--
Palforzia	29	67.3 (62.2, 72.1)	63.7 (52.9, 74.4)	< 0.0001
Placebo	15	3.7 (1.4, 9.1)	--	--

Adapted from 125696/0 Clinical Study Report ARC003 Table 24, Table 14.2.1.31, Table 14.2.1.32, Table 14.2.1.39, Table 14.2.1.40, and Information Request, amendment 17, Table 1

[1]Only 2 subjects identified as American Indian or Alaska Native (1) or Native Hawaiian or other Pacific Islander (1). Due to the small sample size, these subjects were not included in the subgroup analysis. One subject of American Indian or Alaska Native race received Palforzia and was not a responder for the primary endpoint. One subject of Native Hawaiian or Other Pacific Islander race received Palforzia and was considered a responder for the primary efficacy analysis.

<u>Clinical Reviewer comment</u>: Subgroup analysis of the primary efficacy endpoint by geographic region, peanut-specific serum IgE, sex, race and ethnicity demonstrate a consistent response across these groups in Palforzia treated subjects.
While this study was not powered to show a difference between these groups and these analyses were not adjusted for multiplicity, many of the subgroup comparisons had a lower bound which exceeded 15% with p values ≤ 0.0001.

6.1.11.4 Dropouts and/or Discontinuations

Section 6.1.10.1.3 provides a table and summary detailing dropouts and discontinuations for study ARC003.

Please see Section 6.1.10.1.3 and Table 4 for a summary of study dropouts and discontinuations for study ARC003 and the Reviewer Comment for discussion of these data. For the primary and key secondary efficacy endpoints, using the ITT population, subjects who did not have an evaluable exit DBPCFC (e.g. dropped out of the study or discontinued therapy prior to the exit DBPCFC) were considered non-responders/treatment failures.

Clinical Reviewer comment: This reviewer agrees with this conservative approach to accounting for dropouts and discontinuations in the primary and secondary key efficacy endpoint analyses.

6.1.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.1.12 Safety Analyses

6.1.12.1 Methods

A total of 537 subjects were included in the safety population used in the safety analyses presented in this section. Of these, 496 (372 Palforzia and 124 placebo) were pediatric subjects 4 to 17 years of age and 55 were adults 18 to 55 years of age (41 Palforzia and 14 placebo). One pediatric subject in the Palforzia group received incorrect study treatment (a different 300mg kit was dispensed than the one assigned), and as such, this subject was included in the Palforzia treatment group. Two adult subjects in the Palforzia group received the incorrect dose of Palforzia study treatment. However, these 3 subjects were treated with Palforzia and were therefore counted in the Palforzia group for the safety analysis.

Adverse events (AEs) were assessed throughout the study during the entry and exit DBPCFCs, initial up-dosing, dose escalation, and maintenance periods. Allergic symptoms during each dosing period and OFCs were captured using separate forms. Allergic symptoms observed during dosing in clinic visits were recorded on an In-Clinic Dosing form. Safety events related to accidental food exposure were recorded on an Accidental Food exposure form. Episodes of anaphylaxis were recorded on a separate form. Allergic reactions occurring during in-clinic OFCs were recorded on a separate form. Subjects recorded symptoms related to the study treatment daily in electronic diaries. The electronic diary queried for allergic symptoms in a general, open-ended manner and were not graded by subjects. In addition, subjects with gastrointestinal AEs were monitored closely for any symptoms that may indicate development of eosinophilic esophagitis (EoE).

Adverse events were assessed by their intensity, severity, and relation to the study treatment. The CoFAR severity grading scale [2], shown in Table 14, was used for coding allergic reactions and the Muraro grading scale [6], shown in Table 15, was used for grading the severity of anaphylactic reactions. In this review, the term systemic allergic reaction is used for anaphylactic reaction events of any severity and the term

anaphylaxis is used to distinguish anaphylactic reaction events that were severe. The criteria, formulated from expert guidelines [6,17], used to guide the diagnosis of systemic allergic reactions are presented below:

Anaphylaxis is likely when any one of the 3 following sets of criteria is fulfilled:

1. Acute onset of an illness (min to h) with involvement of:
   a. Skin/mucosal tissue (e.g., *generalized* hives, itch or flush, swollen lips/tongue/uvula) *AND*
   b. Airway compromise (e.g., dyspnea, stridor, wheeze/ bronchospasm, hypoxia, reduced PEF) AND/*OR*
   c. Reduced BP or associated symptoms (e.g., hypotonia, syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to the allergen (min to h):
   a. Skin/mucosal tissue (e.g., *generalized* hives, itch/flush, swollen lips/tongue/uvula)
   b. Airway compromise (e.g., dyspnea, stridor wheeze/bronchospasm, hypoxia, reduced PEF)
   c. Reduced BP or associated symptoms (e.g., hypotonia, syncope, incontinence)
   d. *Persistent* GI symptoms (e.g., nausea, vomiting, crampy abdominal pain)

3. Reduced BP after exposure to the allergen (min to h):
   a. Infants and Children: low systolic BP (age-specific) or > 30% drop in systolic BP*
   b. Adults: systolic BP < 90 mm Hg or > 30% drop from their baseline

** Low systolic BP for children is defined as < 70 mmHg from 1 month to 1 year; less than (70 mmHg + [2 x age]) from 1 to 10 years; and < 90 mmHg from age 11 to 17 years.*

Note: Isolated skin or mucosal lesions following the ingestion of a food constitute a "food-induced allergic reaction".

The Common Terminology Criteria for Adverse Events (CTCAE) severity grading scale was used for coding all other AEs. AEs, serious adverse events (SAEs), and deaths were monitored throughout the study.

Symptoms considered to be allergic were graded separately on the following scale:

Table 14: Consortium of Food Allergy Research (CoFAR) Criteria for Grading Allergic Reactions

Grade 1 (Mild)	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Life-Threatening)**	**Grade 5 (Death)**
-Transient or mild discomforts (< 48 hours), no	-Symptoms that produce mild to moderate limitation in activity some assistance may be	-Marked limitation in activity, some assistance usually required; medical intervention/therapy	-Extreme limitation in activity, significant required;	-Death

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-Threatening)	Grade 5 (Death)
or minimal medical intervention /therapy required. -These symptoms may include pruritus, swelling or rash, abdominal discomfort or other transient symptoms.	needed; no or minimal intervention/therapy is required. -Hospitalization is possible. -These symptoms may include persistent hives, wheezing without dyspnea, abdominal discomfort/increased vomiting or other symptoms	required, hospitalization is possible -Symptoms may include bronchospasm with dyspnea, severe abdominal pain, throat tightness with hoarseness, transient hypotension among others. Parenteral medication(s) are usually indicated.	significant medical/therapy. -Intervention is required; hospitalization is probable. Symptoms may include persistent hypotension and/or hypoxia with resultant decreased level of consciousness associated with collapse and/or incontinence or other life-threatening symptoms	

Adapted from 125696/0 Summary of Clinical Safety

Systemic allergic reactions, a collection of allergic symptoms, were graded in totality by the following scale:

Table 15: Grading Criteria for Systemic Allergic Reactions and Anaphylaxis

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)
-skin & subcutaneous tissues, GI, &/or mild respiratory - Flushing, urticaria, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and/or emesis	-mild symptoms + features suggesting moderate respiratory, cardiovascular or GI symptoms - Marked dysphagia, hoarseness and/or stridor; shortness of breath, wheezing & retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness	- hypoxia, hypotension, or neurological compromise - Cyanosis or $SpO_2 \leq 92\%$ at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence

Adapted from 125696/0 Summary of Clinical Safety

The discussion below reflects analyses performed for safety endpoints outlined in Section 6.1.8.

6.1.12.2 Overview of Adverse Events

A total of 367 (98.7%) subjects 4 to 17 years of age receiving Palforzia experienced adverse events. A majority of these were mild (34.7%) to moderate (59.7%). Overall, 118 (95.2%) subjects receiving placebo experienced AEs, the majority of which were also mild (50%) to moderate (44.4%).

In subjects 18 to 55 years of age receiving Palforzia, 41 (100%) experienced AEs compared to 13 (92.9%) subjects in the placebo group. The majority of these in the Palforzia group were mild (29.3%) to moderate (65.9%). In the placebo group, the majority of AEs were also mild (35.7%) to moderate (50%).

The tables below summarize AEs in the safety population by dosing period, divided into pediatric and adult subject groups.

Table 16: Summary of Adverse Events in the Pediatric Safety Population 4 to 17 Years of Age by Dosing Period Including In-Clinic Symptoms: Study ARC003

	Palforzia N (%)	**Placebo N (%)**
Initial Dose Escalation:	--	--
Total Subjects in population	372	124
Subjects with one or more adverse event	189 (50.8)	36 (29.0)
Severity of adverse event:	--	--
Mild	170 (45.7)	33 (26.6)
Moderate	19 (5.1)	3 (2.4)
Severe	0	0
Adverse events leading to study product discontinuation	4 (1.1)	1 (0.8)
Adverse events related to study product	173 (46.5)	27 (21.8)
Subjects with at least one serious adverse event	0	0
Serious adverse events related to study product	0	0
Adverse events related to:	--	--
Anaphylaxis/Systemic allergic reaction	1 (0.3)	0
Allergic reaction	174 (46.8)	28 (22.6)
Accidental food allergen exposure	1 (0.3)	1 (0.8)
Up-Dosing	--	--
Total Subjects in population	366	123
Subjects with one or more adverse event	353 (96.4)	108 (87.8)
Severity of adverse event		
Mild	147 (40.2)	69 (56.1)
Moderate	197 (53.8)	38 (30.9)
Severe	9 (2.5)	1 (0.8)
Adverse events leading to study product discontinuation	35 (9.6)	1 (0.8)
Adverse events related to study product	307 (83.9)	63 (51.2)
Subjects with at least one serious adverse event	4 (1.1)	0
Serious adverse events related to study product	3 (0.8)	0
Adverse events related to:	--	--
Anaphylaxis/Systemic allergic reaction	31 (8.5)	2 (1.6)
Allergic reaction	293 (80.1)	68 (55.3)
Accidental food allergen exposure	54 (14.8)	26 (21.1)
Maintenance		
Total Subjects in population	310	118
Subjects with one or more adverse event	270 (87.1)	94 (79.7)
Severity of adverse event	--	--
Mild	161 (51.9)	57 (48.3)
Moderate	101 (32.6)	37 (31.4)
Severe	8 (2.6)	0

	Palforzia N (%)	Placebo N (%)
Adverse events leading to study product discontinuation	4 (1.3)	0
Adverse events related to study product	159 (51.3)	26 (22.0)
Subjects with at least one serious adverse event	4 (1.3)	1 (0.8)
Serious adverse events related to study product	1 (0.3)	0
Adverse events related to:	--	--
Anaphylaxis/Systemic allergic reaction	27 (8.7)	2 (1.7)
Allergic reaction	169 (54.5)	48 (40.7)
Accidental food allergen exposure	28 (9.0)	24 (20.3)
Overall		
Total Subjects in population	372	124
Subjects with one or more adverse event	367 (98.7)	118 (95.2)
Severity of adverse event	--	--
Mild	129 (34.7)	62 (50.0)
Moderate	222 (59.7)	55 (44.4)
Severe	16 (4.3)	1 (0.8)
Adverse events leading to study product discontinuation	43 (11.6)	2 (1.6)
Adverse events related to study product	328 (88.2)	71 (57.3)
Subjects with at least one serious adverse event	8 (2.2)	1 (0.8)
Serious adverse events related to study product	4 (1.1)	0
Adverse events related to:	--	--
Anaphylaxis/Systemic allergic reaction	53 (14.2)	4 (3.2)
Allergic reaction	325 (87.4)	86 (69.4)
Accidental food allergen exposure	73 (19.6)	41 (33.1)

Adapted from 125696/0 Clinical Study Report ARC003 Table 50

Table 17: Summary of Adverse Events in the Adult Safety Population 18 to 55 Years of Age by Dosing Period including In-Clinic Dosing Symptoms: Study ARC003

	Palforzia N (%)	Placebo N (%)
Initial Dose Escalation:	--	--
Total Subjects in population	41	14
Subjects with one or more adverse event	20 (48.8)	2 (14.3)
Severity of adverse event:	--	--
Mild	19 (46.3)	2 (14.3)
Moderate	1 (2.4)	0
Severe	0	0
Adverse events leading to study product discontinuation	1 (2.4)	0
Adverse events related to study product	20 (48.8)	2 (14.3)
Subjects with at least one serious adverse event	0	0
Serious adverse events related to study product	0	0

	Palforzia N (%)	Placebo N (%)
Adverse events related to:		
Anaphylaxis/Systemic allergic reaction	0	0
Allergic reaction	18 (43.9)	2 (14.3)
Accidental food allergen exposure	0	0
Up-Dosing	--	--
Total Subjects in population	39	14
Subjects with one or more adverse event	38 (97.4)	13 (92.9)
Severity of adverse event		
Mild	14 (35.9)	7 (50.0)
Moderate	23 (59.0)	6 (42.9)
Severe	1 (2.6)	0
Adverse events leading to study product discontinuation	5 (12.8)	0
Adverse events related to study product	35 (89.7)	8 (57.1)
Subjects with at least one serious adverse event	0	0
Serious adverse events related to study product	0	0
Adverse events related to:	--	--
Anaphylaxis/Systemic allergic reaction	4 (10.3)	0
Allergic reaction	33 (84.6)	10 (71.4)
Accidental food allergen exposure	5 (12.8)	2 (14.3)
Maintenance		
Total Subjects in population	25	14
Subjects with one or more adverse event	22 (88.0)	8 (57.1)
Severity of adverse event		
Mild	8 (32.0)	4 (28.6)
Moderate	13 (52.0)	3 (21.4)
Severe	1 (4.0)	1 (7.1)
Adverse events leading to study product discontinuation	1 (4.0)	0
Adverse events related to study product	13 (52.0)	1 (7.1)
Subjects with at least one serious adverse event	2 (8.0)	1 (7.1)
Serious adverse events related to study product	1 (4.0)	0
Adverse events related to:	--	--
Anaphylaxis/Systemic allergic reaction	5 (20.0)	1 (7.1)
Allergic reaction	14 (56.0)	4 (28.6)
Accidental food allergen exposure	4 (16)	3 (21.4)
Overall	--	--
Total Subjects in population	41	14
Subjects with one or more adverse event	41 (100.0)	13 (92.9)
Severity of adverse event	--	--
Mild	12 (29.3)	5 (35.7)
Moderate	27 (65.9)	7 (50.0)
Severe	2 (4.9)	1 (7.1)
Adverse events leading to study product discontinuation	7 (17.1)	0 (0.0)
Adverse events related to study product	38 (92.7)	10 (71.4)

	Palforzia N (%)	Placebo N (%)
Subjects with at least one serious adverse event	2 (4.9)	1 (7.1)
Serious adverse events related to study product	1 (2.4)	0
Adverse events related to:	--	--
Anaphylaxis/Systemic allergic reaction	8 (19.5)	1 (7.1)
Allergic reaction	36 (87.8)	11 (78.6)
Accidental food allergen exposure	8 (19.5)	4 (28.6)

Adapted from 125696/0 Clinical Study Report ARC003 Table 14.3.1.15.4

Clinical Reviewer comment: The pattern of AE reporting is similar to the data in the Integrated Summary of Safety (ISS). Please see section 8.4 for a discussion of AEs in the controlled study population.

Common Adverse Events

Below are tables summarizing common AEs by preferred term for both pediatric and adult safety populations during Up-Dosing and Maintenance periods. These periods comprised the majority of the safety evaluation (the initial dose escalation lasted 2 days) and are therefore representative of the safety events occurring in the safety population for study ARC003.

Table 18: Summary of Common Adverse Events in at Least 5% of the Pediatric Safety Population 4 to 17 Years of Age Including In-Clinic Symptoms by Preferred Term: Study ARC003

	Palforzia N (%)	Placebo N (%)
Up-Dosing:	--	--
Total Subjects in population	366	123
Abdominal pain	156 (42.6)	25 (20.3)
Vomiting	127 (34.7)	22 (17.9)
Pruritus	117 (32.0)	25 (20.3)
Upper abdominal pain	136 (37.2)	17 (13.8)
Cough	117 (32.0)	30 (24.4)
Throat irritation	131 (35.8)	26 (21.1)
Oral pruritus	131 (35.8)	15 (12.2)
Nausea	128 (35.0)	22 (17.9)
Urticaria	115 (31.4)	23 (18.7)
Rhinorrhea	82 (22.4)	25 (20.3)
Sneezing	76 (20.8)	15 (12.2)
Throat tightness	70 (19.1)	6 (4.9)
Rash	61 (16.7)	15 (12.2)
Oral Paresthesia	57 (15.6)	5 (4.1)
Anaphylactic reaction	31 (8.5)	2 (1.6)
Dyspnea	32 (8.7)	3 (2.4)
Lip swelling	25 (6.8)	3 (2.4)
Dysphonia	19 (5.2)	2 (1.6)
Chest discomfort	19 (5.2)	1 (0.8)
Maintenance	--	--
Total Subjects in population	310	118
Abdominal pain	46 (14.8)	7 (5.9)
Vomiting	50 (16.1)	14 (11.9)
Pruritus	45 (14.5)	14 (11.9)

	Palforzia N (%)	Placebo N (%)
Abdominal pain upper	41 (13.2)	9 (7.6)
Cough	61 (19.7)	22 (18.6)
Throat irritation	43 (13.9)	11 (9.3)
Oral pruritus	39 (12.6)	5 (4.2)
Nausea	45 (14.5)	8 (6.8)
Urticaria	63 (20.3)	17 (14.4)
Rhinorrhea	46 (14.8)	9 (7.6)
Sneezing	33 (10.6)	5 (4.2)
Throat tightness	20 (6.5)	0
Rash	24 (7.7)	7 (5.9)
Oral Paresthesia	23 (7.4)	2 (1.7)
Anaphylactic reaction	27 (8.7)	2 (1.7)
Dyspnea	17 (5.5)	1 (0.8%)
Lip swelling	13 (4.2)	2 (1.7)
Dysphonia	8 (2.6)	1 (0.8)
Chest discomfort	8 (2.6%	0
Overall	--	--
Total Subjects in population	372	124
Abdominal pain	194 (52.2)	30 (24.2)
Vomiting	154 (41.4)	30 (24.2)
Pruritus	153 (41.1)	34 (27.4)
Abdominal pain upper	152 (40.9)	26 (21.0)
Cough	152 (40.9)	42 (33.9)
Throat irritation	152 (40.9)	34 (27.4)
Oral pruritus	151 (40.6)	20 (16.1)
Nausea	146 (39.2)	29 (23.4)
Urticaria	143 (38.4)	30 (24.2)
Rhinorrhea	113 (30.4)	28 (22.6)
Sneezing	98 (26.3)	18 (14.5)
Throat tightness	86 (23.1)	8 (6.5)
Rash	81 (21.8)	18 (14.5)
Oral Paresthesia	65 (17.5)	8 (6.5)
Anaphylactic reaction	53 (14.2)	4 (3.2)
Dyspnea	44 (11.8)	5 (4.0)
Lip swelling	38 (10.2)	5 (4.0)
Dysphonia	25 (6.7)	2 (1.6)
Chest discomfort	24 (6.5)	1 (0.8)

Adapted from 125696/0 Clinical Study Report ARC003 Table 51

Table 19: Summary of Common Adverse Events in at Least 5% of the Adult Safety Population 18 to 55 Years of Age Including In-Clinic Symptoms by Preferred Term: Study ARC003

	Palforzia N (%)	Placebo N (%)
Up-Dosing:	--	--
Total Subjects in population	39	14
Abdominal pain	20 (51.3)	3 (21.4)
Vomiting	4 (10.3)	0
Pruritus	12 (30.8)	2 (14.3)
Upper abdominal pain	14 (35.9)	4 (28.6)
Cough	11 (28.2)	2 (14.3)
Throat irritation	12 (30.8)	2 (14.3)
Oral pruritus	14 (35.9)	2 (14.3)
Nausea	20 (51.3)	3 (21.4)

	Palforzia N (%)	Placebo N (%)
Urticaria	8 (20.5)	2 (14.3)
Rhinorrhea	9 (23.1)	3 (21.4)
Sneezing	13 (33.3)	3 (21.4)
Throat tightness	11 (28.2)	1 (7.1)
Rash	0	0
Oral paresthesia	13 (33.3)	1 (7.1)
Anaphylactic reaction	4 (10.3)	0
Dyspnea	10 (25.6)	3 (21.4)
Lip swelling	2 (5.1)	0
Dysphonia	5 (12.8)	0
Chest discomfort	2 (5.1)	0
Maintenance	--	--
Total Subjects in population	25	14
Abdominal pain	1 (4.0)	1 (7.1)
Vomiting	4 (16.0)	2 (14.3)
Pruritus	4 (16.0)	0
Upper Abdominal pain	4 (16.0)	0
Cough	1 (4.0)	1 (7.1)
Throat irritation	2 (8.0)	0
Oral pruritus	6 (24.0)	2 (14.3)
Nausea	3 (12.0)	0
Urticaria	4 (16.0)	1 (7.1)
Rhinorrhea	0	0
Sneezing	2 (8.0)	0
Throat tightness	1 (4.0)	0
Rash	0	0
Oral Paresthesia	3 (12.0	0
Anaphylactic reaction	5 (20.0	1 (7.1)
Dyspnea	0	0
Lip swelling	0	0
Dysphonia	1 (4.0	0
Chest discomfort	1 (4.0	0
Overall	--	--
Total Subjects in population	41	14
Abdominal pain	18 (43.9)	6 (42.9)
Vomiting	5 (12.2)	3 (21.4)
Pruritus	16 (39.0)	2 (14.3)
Upper abdominal pain	16 (39.0)	4 (28.6)
Cough	12 (29.3)	3 (21.4)
Throat irritation	12 (29.3)	2 (14.3)
Oral pruritus	15 (36.6)	4 (28.6)
Nausea	20 (48.8)	3 (21.4)
Urticaria	12 (29.3)	3 (21.4)
Rhinorrhea	11 (26.8)	3 (21.4)
Sneezing	14 (34.1)	3 (21.4)
Throat tightness	12 (29.3)	2 (14.3)
Rash	2 (4.9)	0
Oral Paresthesia	15 (36.6)	1 (7.1)
Anaphylactic reaction	8 (19.5)	1 (7.1)
Dyspnea	10 (24.4)	3 (21.4)
Lip swelling	2 (4.9)	0
Dysphonia	6 (14.6)	0
Chest discomfort	3 (7.3)	0

Adapted from 125696/0 Clinical Study Report ARC003 Table 14.3.1.16.4

Severe Adverse Events

Below is a tabular summary of treatment-related severe adverse events (grade 3) for the pediatric safety populations during Up-Dosing and Maintenance periods. No pediatric subjects had a severe treatment-related adverse event during Initial Dose Escalation. No pediatric subject had a grade 4 or 5 adverse event or symptom in either the Palforzia or placebo group. No pediatric subject in the placebo group experienced a severe adverse event related to the study treatment. No adult subject in either treatment group had a grade 4 or 5 adverse event or symptom. No adult subject had a severe treatment-related adverse event during Initial Dose Escalation. Only 1 of 39 adult subjects (2.6%) had a grade 3, severe treatment-related symptom (urticaria) during Up-Dosing.

Table 20: Summary of Treatment-Related Severe Adverse Events in the Pediatric Safety Population 4 to 17 Years of Age Including In-Clinic Symptoms: Study ARC003

	Palforzia N (%)	**Placebo N (%)**
Up-Dosing	--	--
Total Subjects in population	366	123
Subjects with one or more severe adverse event	6 (1.6)	0
Urticaria	1 (0.3)	0
Pruritus	1 (0.3)	0
Upper abdominal pain	2 (0.5)	0
Nausea	2 (0.5)	0
Ear pruritus	1 (0.3)	0
Ocular hyperemia	0	0
Anaphylactic reaction	0	0
Dysphonia	0	0
Rhinorrhea	0	0
Flushing	0	0
Maintenance	--	--
Total Subjects in population	310	118
Subjects with one or more severe adverse event	3 (1.0)	0
Urticaria	2 (0.6)	0
Pruritus	1 (0.3)	0
Upper abdominal pain	0	0
Nausea	0	0
Ear pruritus	0	0
Ocular hyperemia	1 (0.3)	0
Anaphylactic reaction	1 (0.3)	0
Dysphonia	1 (0.3)	0
Rhinorrhea	1 (0.3)	0
Flushing	1 (0.3)	0
Overall	--	--
Total Subjects in population	372	124
Subjects with one or more severe adverse event	9 (2.4)	0
Urticaria	3 (0.8)	0
Pruritus	2 (0.5)	0
Upper abdominal pain	2 (0.5)	0
Nausea	2 (0.5)	0
Ear pruritus	1 (0.3)	0
Ocular hyperemia	1 (0.3)	0
Anaphylactic reaction	1 (0.3)	0
Dysphonia	1 (0.3)	0

	Palforzia N (%)	Placebo N (%)
Rhinorrhea	1 (0.3)	0
Flushing	1 (0.3)	0

Adapted from 125696/0 Clinical Study Report ARC003 Table 55

Subjects with Asthma

Study ARC003 included subjects with asthma. Subjects with severe asthma or subjects whose asthma was uncontrolled or difficult to control were excluded from the study. Please see Section 6.1.3 for the eligibility criteria. In the pediatric population of subjects 4 to 17 years of age, 53% (263/496) of subjects had a diagnosis of asthma. Of this group, 198 received Palforzia and 65 placebo (53.2% vs 52.4% respectively). Adverse events in subjects with asthma (99.0% Palforzia and 96.9% placebo) were similar to those without a clinical history of asthma (98.3% and 93.2%). See Table 21.

The overall incidence of systemic allergic reaction in Palforzia-treated subjects with asthma was 13.6% and without asthma was 14.9%. The overall incidence of systemic allergic reaction in placebo-treated subjects with asthma was 3.1% and without asthma was 3.4%.

Of the 36 adult subjects with asthma, 24 received Palforzia and 12 received placebo; of adult subjects without asthma, 17 received Palforzia and 2 received placebo. There was no discernable difference in the number of AEs in the small number of adult asthmatics compared to pediatric asthmatics.

Table 21: Summary of Common Adverse Events in Asthmatics and Non-Asthmatics in at Least 5% of the Pediatric Safety Population 4 to 17 Years of Age Including In-Clinic Symptoms by Preferred Term: Study ARC003

	Palforzia N (%) With asthma	Placebo N (%) With asthma	Palforzia N (%) Without asthma	Placebo N (%) Without asthma
Initial Dose Escalation:	--	--	--	--
Total subjects in population	198	65	174	59
Abdominal pain	51 (25.8)	5 (7.7)	32 (18.4)	3 (5.1)
Upper abdominal pain	5 (2.5)	2 (3.1)	4 (2.3)	1 (1.7)
Nausea	20 (10.1)	0	11 (6.3)	1 (1.7)
Oral Pruritus	19 (9.6)	2 (3.1)	17 (9.8)	6 (10.2)
Throat irritation	15 (7.6)	5 (7.7)	13 (7.5)	0
Pruritus	14 (7.1)	3 (4.6)	11 (6.3)	5 (8.5)
Throat tightness	11 (5.6)	3 (4.6)	3 (1.7)	0
Vomiting	11 (5.6)	0	4 (2.3)	0
Sneezing	8 (7.0)	0	8 (4.6)	3 (5.1)
Urticaria	6 (3.0)	2 (3.1)	10 (5.7)	1 (1.7)
Asthma	2 (1.0)	0	0	0
Wheezing	2 (1.0)	0	0	0
Dyspnea	2 (1.0)	1 (1.5)	1 (0.6)	0
Anaphylaxis/Systemic allergic reaction	1 (0.5)	0	0	0
Up-Dosing:	--	--	--	--
Total subjects in population	192	64	174	59

	Palforzia N (%) With asthma	Placebo N (%) With asthma	Palforzia N (%) Without asthma	Placebo N (%) Without asthma
Abdominal pain	86 (44.8)	11 (17.2)	70 (40.2)	14 (23.7)
Upper abdominal pain	77 (40.1)	9 (14.1)	59 (33.9)	8 (13.6)
Nausea	76 (39.6)	7 (9.4)	52 (29.9)	16 (27.1)
Vomiting	75 (39.1)	7 (10.9)	52 (29.9)	15 (25.4)
Oral pruritus	67 (34.9)	5 (7.8)	64 (36.8)	10 (16.9)
Throat irritation	63 (32.8)	14 (21.9)	68 (39.1)	12 (20.3)
Pruritus	62 (32.3)	12 (18.8)	55 (31.6)	13 (22.0)
Urticaria	61 (31.8)	9 (14.1)	54 (31.0)	14 (23.7)
Cough	55 (28.6)	16 (25)	62 (35.6)	14 (23.7)
Asthma	24 (12.5)	4 (6.3)	0	0
Wheezing	24 (12.5)	4 (6.3)	20 (11.5)	3 (5.1)
Dyspnea	21 (10.9)	3 (4.7)	11 (6.3)	0
Anaphylaxis/Systemic allergic reaction	16 (8.3)	1 (1.6)	15 (8.6)	1 (1.7)
Maintenance	--	--	--	--
Total subjects in population	156	61	154	57
Cough	30 (19.2)	11 (18)	31 (20.1)	11 (19.3)
Vomiting	30 (19.2)	7 (11.5)	20 (13.0)	7 (12.3)
Urticaria	28 (17.9)	6 (9.8)	35 (22.7)	11 (19.3)
Nausea	24 (15.4)	6 (9.8)	17 (11.0)	2 (3.5)
Abdominal pain	24 (15.4)	5 (8.2)	22 (14.3)	2 (3.5)
Pruritus	20 (12.8)	9 (14.8)	25 (16.2)	5 (8.8)
Asthma	19 (12.2)	6 (9.8)	0	0
Wheezing	13 (8.3)	6 (9.8)	6 (3.9)	4 (7.0)
Dyspnea	12 (7.7)	1 (1.6)	5 (3.2)	0
Anaphylaxis/Systemic allergic reaction	12 (7.7)	1 (1.6)	15 (9.7)	1 (1.8)

Adapted from 125696/0 Clinical Study Report ARC003 Table 77 and Table 78

Clinical Reviewer comment: As expected, respiratory AEs were increased overall in subjects with asthma (in both the treatment and placebo groups) compared to subjects without asthma. Subjects with asthma overall reported more respiratory AEs compared to placebo subjects with a history of asthma. No substantial increase in systemic allergic reactions is seen in Palforzia treated subjects with asthma compared to those without asthma. Palforzia does appear to substantially increase the risk of allergic reactions in subjects with asthma enrolled in the study.

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

Serious adverse events (SAEs) of systemic allergic reactions and anaphylaxis are discussed in Section 6.1.12.5 below. For all subjects 4 to 55 years of age in study ARC003, 12 subjects experienced SAEs, 10 in the Palforzia group and 2 in the placebo group. All of these events occurred during Up-Dosing and Maintenance periods. A SAE in the placebo group, a humerus fracture, was considered unrelated. All of these events resolved by the end of the study. In the pediatric population 4 to 17 years of age, 8 (2.2%) subjects in the Palforzia group had SAEs and 1 (0.8%) placebo treated subject had an SAE during the study. These included systemic allergic reactions (3),

gastroenteritis (2), pharyngitis (1), asthma (2), and concussion (1) in the Palforzia group. The 3 events of anaphylactic reaction and one event of asthma were considered related to the study treatment in the Palforzia group ((1.1%) 4/372). The placebo subject reported a Humerus fracture.

In the adult population 2 subjects in the Palforzia group had an SAE and 1 in the placebo group. These events were anaphylactic reaction (1) and syncope (1) in the Palforzia group and cutaneous vasculitis (1) in the placebo group. One of these events was considered related: an anaphylactic reaction to Palforzia during the maintenance period that led to permanent discontinuation.

Clinical Reviewer comment: This reviewer agrees with the assessment of relatedness of the product with the SAEs as above. In particular, this reviewer agrees that one of the SAEs of asthma is unrelated as it occurred in the context of a viral upper respiratory illness (URI). The unrelated episode of asthma occurred in a 5 year old female undergoing up-dosing on 3mg Palforzia who developed URI with subsequent viral testing positive for rhinovirus. No signs or symptoms were suggestive of a systemic allergic reaction. Palforzia was temporarily withheld. The subject was ultimately able to complete the course of Palforzia and ingested a maximum dose of 1000mg peanut protein with no more than mild symptoms during the exit DBPCFC.

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESIs) were pre-specified and included anaphylaxis and prolonged gastrointestinal symptoms that may indicate development of eosinophilic esophagitis (EoE). Use of epinephrine as a rescue medication during the study period (excluding oral food challenges) is also considered an AESI for the purposes of this review.

Anaphylaxis and Systemic Allergic Reactions

For study ARC003, the Palforzia group reported more systemic allergic reactions (14.2%) compared to placebo (3.2%) in subjects 4 to 17 years of age. For the Palforzia group, 23/372 (6.2%) had mild reactions, and 29/372 (7.8%) had moderate reactions. One reported a severe reaction. This subject consumed 300mg Palforzia at work and approximately 20 minutes later developed anaphylaxis. The subject used epinephrine about 15 minutes later and went home but required another dose of epinephrine and was transported to the hospital. In total, the subject received 3 doses of epinephrine and the event resolved. No co-factors were associated with this event. This event was reported as an SAE.

Adult (18 to 55 years of age) Palforzia recipients reported more systemic allergic reactions (8/41 (19.5%)) compared to adult placebo recipients (1/14 (7.1%)). In adult Palforzia recipients, 8/41 (19.5%) subjects in the Palforzia group had systemic allergic reactions: 3 during up-dosing and 4 during maintenance. One of these subjects had 2 reactions, 1 during up-dosing and 1 during maintenance. The single placebo subject who reported a systemic reaction had a reaction related to an accidental food exposure. This event was graded as moderate and did not require treatment with epinephrine. No adult subject reported a severe systemic allergic reaction.

Table 22: Systemic Allergy Reactions by Severity in the Pediatric Safety Population 4 to 17 Years of Age Including In-Clinic Symptoms by Preferred Term: Study ARC003

	Palforzia N (%)	**Placebo N (%)**
Initial Dose Escalation:	--	--
Total subjects in population	372	124
Severity	--	--
Mild	1 (0.3)	0
Moderate	0	0
Severe (Anaphylaxis)	0	0
Up-Dosing:	--	--
Total subjects in population	366	123
Severity	--	--
Mild	13 (3.6)	1 (0.8)
Moderate	18 (4.9)	1 (0.8)
Severe (Anaphylaxis)	0	0
Maintenance	--	--
Total subjects in population	310	118
Severity		
Mild	12 (3.9)	0
Moderate	14 (4.5)	2 (1.7)
Severe (Anaphylaxis)	1 (0.3)	0
Overall	--	--
Total subjects in population	372	124
Severity	--	--
Mild	23 (6.2)	1 (0.8)
Moderate	29 (7.8)	3 (2.4)
Severe (Anaphylaxis)	1 (0.3)	0

Adapted from 125696/0 Clinical Study Report ARC003 Table 63

Clinical Reviewer comment: As expected, more subjects ingesting Palforzia (which contains peanut protein, a substance to which study participants are allergic) experienced systemic allergic reactions compared to placebo. Analysis of systemic allergic reactions in Palforzia recipients in the ITT population compared to recipients in the completer population (those who completed the exit DBPCFC) reveals 14.2% vs 11.8% overall, respectively. During up-dosing, 8.5% vs. 6.4% reported systemic allergic reactions and 8.7% vs. 7.1% reported reactions during the maintenance period. While limited by small numbers, these data suggest that subjects included in the ITT population who received Palforzia and dropped out or did not complete the exit DBPCFC were less tolerant (e.g. reported more systemic allergic reactions regardless of severity) to the study product than those in the completer population.

Use of Epinephrine

In the pediatric subgroup, 52 (14.0%) subjects in the Palforzia group versus 8 (6.5%) subjects in the placebo group used epinephrine at least once. Most of these episodes occurred at home as opposed to at the study sites (67.1% Palforzia vs. 88.9% placebo) and were associated with mild to moderate AEs. In adults, 1 (2.6%) subject used epinephrine during up-dosing with Palforzia and 3 (12%) during maintenance dosing with Palforzia. No placebo subjects used epinephrine. Overall, a total of 12 subjects (4 to 55 years of age) discontinued due to adverse events that required epinephrine use.

Table 23: Summary of Use of Epinephrine in in the Pediatric Safety Population 4 to 17 Years of Age: Study ARC003

	Palforzia N (%)	Placebo N (%)
Initial Dose Escalation:	--	--
Total subjects in population	372	124
Subjects with any use of epinephrine	6 (1.6)	0
Age subcategory	--	--
4-11 years	5 (1.3)	0
12-17 years	1 (0.3)	0
Number of epinephrine doses per episode	--	--
1 dose	6	0
2 doses	0	0
≥3 doses	0	0
Severity of AE associated with the episode	--	--
Grade 1	3	0
Grade 2	3	0
Grade 3	0	0
Grade 4	0	0
Grade 5	0	0
Location of episode	--	--
Home	0	0
Study site	6	0
Up-Dosing:	--	--
Total subjects in population	366	123
Subjects with any use of epinephrine	35 (9.6)	5 (4.1)
Age subcategory	--	--
4-11 years	22 (6)	3 (2.4)
12-17 years	13 (3.6)	2 (1.6)
Number of epinephrine doses per episode	--	--
1 dose	43	5
2 doses	4	0
≥3 doses	0	0
Severity of AE associated with the episode	--	--
Grade 1	18	2
Grade 2	25	3
Grade 3	1	0
Grade 4	0	0
Grade 5	0	0
Location of episode	--	--
Home	29	5
Study site	18	0
Maintenance	--	--
Total subjects in population	310	118
Subjects with any use of epinephrine	24 (7.7)	4 (3.4)
Age sub category	--	--
4-11 years	10 (3.2)	4 (3.4)
12-17 years	14 (4.5)	0
Number of epinephrine doses per episode	--	--
1 dose	27	4
2 doses	1	0
≥3 doses	1	0
Severity of AE associated with the episode	--	--
Grade 1	12	2
Grade 2	16	2
Grade 3	1	0
Grade 4	0	0

	Palforzia N (%)	Placebo N (%)
Grade 5	0	0
Location of episode	--	--
Home	26	3
Study site	3	1
Overall	--	--
Total subjects in population	372	124
Subjects with any use of epinephrine	52 (14.0)	8 (6.5)
Age sub category	--	--
4-11 years	29 (7.8)	6 (4.8)
12-17 years	23 (6.2)	2 (1.6)
Number of epinephrine doses per episode	--	--
1 dose	76	9
2 doses	5	0
≥3 doses	1	0
Severity of AE associated with the episode	--	--
Grade 1	33	4
Grade 2	44	5
Grade 3	2	0
Grade 4	0	0
Grade 5	0	0
Location of episode	--	--
Home	55	8
Study site	27	1

Adapted from 125696/0 Clinical Study Report ARC003 Table 75

Clinical Reviewer comment: Subjects treated with Palforzia have increased epinephrine use compared to placebo over all periods of study ARC003 including the maintenance period. Most of the reactions occurred at home, required only one dose of epinephrine to treat and most reactions were mild to moderate. In clinical practice, patients are asked to administer injectable epinephrine early – as soon as there is any concern for an allergic reaction – reinforcing the findings of this study, that most AEs associated with epinephrine use are mild to moderate. Also notable are the numerous uses of epinephrine that occurred in clinic, particularly during up-dosing, demonstrating that the first dose of each new dose level puts subjects at risk for a reaction. Similar data were noted in adults 18-55 years of age.

The goal of Palforzia treatment is to increase the amount of peanut protein ingested with no more than minimal allergic symptoms in an effort to protect against accidental exposures. The study met the primary efficacy endpoint demonstrating Palforzia treatment is capable of producing this effect; however, the study treatment causes increased allergic reactions in subjects compared to only a simple avoidance diet followed by the placebo group. The Palforzia benefit risk assessment is discussed in Section 11 of this document.

Gastrointestinal Adverse Events and Eosinophilic Esophagitis

Gastrointestinal (GI) disorders were the most common system organ class (SOC) of AEs overall (85.8% Palforzia vs 69.4% placebo). The most common with an at least 5% higher incidence in the Palforzia group in decreasing order were abdominal pain,

vomiting, upper abdominal pain, oral pruritus, nausea, oral paresthesia, and lip swelling. No SAE was a GI event. All discontinuations due to GI events occurred during up-dosing. Sixteen (4.3%) subjects discontinued due to GI adverse events that were chronic or recurrent. Of these, abdominal pain and vomiting were the most common GI adverse events leading to discontinuation (each in 1.6% of the Palforzia recipients) followed by upper abdominal pain and nausea (each in 1.3% of the Palforzia recipients).

The development of eosinophilic esophagitis (EoE) was of particular interest because subjects ingesting oral immunotherapy may be at higher risk for this disease. Overall, the incidence of EoE in this study was low. Only 1 subject in the pediatric age group (treated with Palforzia) developed biopsy-confirmed EoE (1/372 (0.3%)). Please see Section 8.4.8 for further discussion of all cases of EoE in the clinical program.

6.1.12.6 Clinical Test Results

Not applicable.

6.1.12.7 Dropouts and/or Discontinuations

Out of 555 randomized subjects 4 to 55 years of age, 106 discontinued from the Palforzia group. The most common reasons were withdrawal of consent, adverse event, and up-dosing failure. In the placebo group, 12 discontinued. The most common reasons were withdrawal of consent and adverse event.

Please see Section 6.1.10.1.3 for a tabular summary of subject disposition.

Clinical Reviewer comment: Palforzia recipients discontinued ARC003 at a higher rate than placebo recipients. Had subjects who discontinued due to adverse events stayed in the study, adverse event rates for Palforzia recipients may have been higher, particularly through the maintenance period. This imbalance in discontinuation follows the imbalance in the adverse event profile. Both have been noted and considered during review of the safety profile for this product.

6.1.13 Study Summary and Conclusions

Study ARC003 was a phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of Palforzia oral immunotherapy in children and adult subjects 4 to 55 years of age with confirmed IgE-mediated peanut allergy. The population evaluated for the indication was children 4 to 17 years of age (N = 496). The majority of enrolled subjects were white males. Subjects were enrolled from North America. The presence of other atopic conditions such as food allergies other than peanut or atopic dermatitis/eczema were balanced evenly between treatment arms. A small number of adult subjects 18-55 years of age were randomized into ARC003 (N=56), the majority from North America (78%).

Of the 499 pediatric subjects who were randomized 18% discontinued overall with 21.4% of Palforzia recipients vs. 8.0% of placebo recipients discontinuing due to adverse events and withdrawal of consent. Adult Palforzia recipients discontinued at a higher rate (52.4% vs. 7.1%, Palforzia compared to placebo, respectively) compared to pediatric subjects due to adverse events and withdrawal of consent.

The study met the pre-specified criterion for success on the primary endpoint: the proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 600 mg of peanut protein with no more than mild symptoms at the Exit DBPCFC with a lower bound of the corresponding 95% CI being >15%. The result was: 63.2% 95% CI (53.0, 73.3). The small number of adult participants precluded an accurate assessment of the efficacy in adults, however, those results trended towards a positive Palforzia treatment effect.

Palforzia recipients reported more adverse events overall including systemic allergic reactions (14.2% Palforzia vs. 3.2% placebo, overall) and use of epinephrine as a rescue medication (14.0% Palforzia vs. 6.5% placebo) at least once. The majority of these events were mild to moderate. No deaths occurred in the study. SAEs occurred more frequently in the treatment arm, 4 of which were related to the study product ((1.1%) 4/372).

Using the primary endpoint, it is reasonable to infer a clinical benefit because Palforzia recipients tolerated an increased dose of peanut protein with no more than mild symptoms compared to at baseline during the study entry OFC. The increased ability to tolerate peanut during the exit OFC implies that subjects could experience no more than mild allergic symptoms upon accidental exposure to food contaminated with amounts of 600mg or less of peanut protein. Palforzia recipients experienced more systemic allergic reactions to the study product. These events are expected in peanut allergic subjects upon increasing exposure to peanut protein as performed in the ARC003 protocol. The available efficacy and safety data from this study support the approval of Palforzia in pediatric subjects 4 to 17 years of age with proper risk mitigation strategies in place. See Section 11 for a discussion of the benefit-risk profile for Palforzia.

6.2 Study ARC007

Study title: Real-World Market-Supporting Experience Study in Peanut-Allergic Children Ages 4 to 17 Years (RAMSES)

Clinical Reviewer comment: ARC007 was conducted to supplement the safety database of main efficacy study, ARC003. In previous discussions with the applicant (letter from CBER faxed January 13, 2017), CBER stated that, ideally, the pediatric safety database would include at least 600 pediatric subjects (from both ARC003 and ARC007) exposed to the dose and formulation evaluated for licensure. ARC007 was conducted to address this request and increase the size of the safety database.

6.2.1 Objectives and Endpoints:

Primary Objective: To assess the safety and tolerability of the oral immunotherapy regimen for 6 months in peanut-allergic children.

Secondary Objectives: To characterize the frequency of all treatment-related AEs by study period, especially those of interest (anaphylaxis, GI-related AEs, accidental food allergen exposure; severe AEs, and AEs associated with the use of epinephrine), asthma control and exploratory immune parameters.

Primary Endpoint: Frequency of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs), during the overall study period.

Secondary Endpoints:

1. Frequency of premature discontinuation of dosing due to AEs; and frequency of premature discontinuation of dosing due to chronic/recurrent GI AEs
2. Proportion of chronic / recurrent GI AEs resolving at 2, 4, and ≥ 12 weeks following cessation of dosing
3. Frequency of allergic reaction (hypersensitivity) AEs occurring during up-dosing, normalized for duration of treatment
4. Frequency of anaphylaxis as defined in the protocol, according to the International Consensus (ICON) on anaphylaxis
5. Frequency of use of epinephrine as a rescue medication
6. Frequency of accidental ingestions of peanut and other allergenic foods and severity of any resultant reactions
7. Assessment of asthma control using the Asthma Control Test questionnaire and frequency of use of asthma rescue medication (short acting beta-agonists) in subjects with asthma

Exploratory Endpoints:

8. Changes in peanut-specific and peanut component-specific serum IgE and IgG4 levels
9. Changes in peanut skin prick test (SPT) mean wheal diameters
10. Changes in scores of food allergy related quality of life questionnaire (FAQLQ), and the food allergy independent measure (FAIM) questionnaire.

6.2.2 Study Design

ARC007 was a phase 3, randomized, double-blind, placebo-controlled, multicenter safety study conducted at 64 sites (59 located in the US). Peanut allergic children 4 to 17 years of age (N=506) were randomized (2:1) to Palforzia or placebo. Demographics were balanced between the treatment groups and comparable to the demographics in ARC003; most subjects were white, male, 4 to 11 years of age, and had other atopic conditions including asthma, allergic rhinitis, atopic dermatitis, and food allergy other than peanut. Eligibility criteria were the same as for ARC003 with the exception of no entry DBPCFC and different criteria for skin prick testing and peanut specific serum IgE values. Subjects underwent initial dose escalation and up-dosing to 300mg Palforzia. Subjects continued 300mg Palforzia for two weeks before the study end; ARC007 did not include a maintenance period. The procedures for safety data collection in ARC007 mirrored that of ARC003 which allowed for integration of safety data between these two studies. No exit DBPCFC was done because ARC007 was a safety study; an efficacy assessment was not part of the study design.

Safety evaluations in ARC007 revealed a similar imbalance of study discontinuations, systemic allergic reactions, and epinephrine use in Palforzia recipients compared to placebo recipients when compared to study ARC003. Overall, 23% (78/338) of Palforzia

recipients discontinued compared to placebo (5.9% (10/168)). The most common reasons for discontinuation in the Palforzia group were AEs (primarily due to GI or allergic AEs) and withdrawal of consent. The most comment AEs reported overall were GI-related and occurred with greater frequency in the Palforzia group (87.8% Palforzia vs. 57.1% placebo). Systemic allergic reactions were more frequent overall in Palforzia recipients compared to placebo (10.7% vs. 5.4%, respectively). The majority of reactions were related to the study product. Epinephrine use as a rescue medication followed this trend, with 11% of Palforzia recipients compared to 5.4% of placebo recipients reporting at least 1 administration of epinephrine. Two Palforzia treated subjects reported cases of EoE, while no placebo subjects reported EoE. One death, a craniocerebral injury due to a motor vehicle accident, occurred in the placebo group. This injury was not related to the study treatment. Four SAEs occurred during the study, all unrelated to the study treatment. In the Palforzia group there was 1 event of lymphocytic leukemia and 1 event of mycoplasma pneumonia. In the placebo group there was 1 craniocerebral injury (noted above) and 1 event of appendicitis.

Clinical Reviewer comment: In addition to safety, an aim of study ARC007 was to define stringent criteria that a community-based clinical allergist might use to diagnose peanut allergy with a high level of confidence without using an OFC. Therefore, ARC007 included subjects who had a history of physician-diagnosed IgE-mediated peanut allergy that includes the onset of characteristic allergic signs and symptoms within two hours of known oral exposure to peanut or a peanut-containing food, mean peanut wheal on skin prick test of at least 8 mm greater than the negative saline control and serum IgE to peanut of at least 14 kUA/L at screening. The diagnostic criteria used in ARC007 were more stringent than the criteria for skin prick testing and serum IgE to peanut used in ARC003 (serum IgE to peanut ≥ 0.35 kUA/L and/or a skin prick test to peanut ≥ 3 mm compared with control) because ARC007 did not require an OFC for study entry. These limits were chosen based on the sensitivity and specificity of these tests for the diagnosis of IgE-mediated peanut allergy [8] to reduce the possibility that subjects who did not have a true peanut allergy enrolled in the study as this could result in data that do not adequately inform the safety of this product in persons at highest risk for adverse reactions to this product.

Review of the safety data from ARC007 does not reveal any major differences compared to trends in ARC003, therefore detailed data are not presented. The integrated safety poolings were used to provide a comprehensive presentation of the safety data from this program (see Section 8).

6.3 Study ARC001

Study title: Oral Desensitization to Peanut in Peanut-Allergic Children and Adults using Characterized Peanut Allergen (CPNA) Oral Immunotherapy (OIT)

6.3.1 Objectives and Endpoints

Primary objective: The primary objective is to demonstrate the efficacy of Characterized Peanut Allergen through reduction in clinical reactivity to limited amounts of peanut allergen in peanut-allergic children and young adults (ages 4-26 years, inclusive).

Secondary objectives:

1. To demonstrate the safety of Characterized Peanut Allergen as measured by incidence of adverse events and dosing symptoms.
2. To evaluate the immunological effects of peanut OIT therapy.
3. To determine the time course of tolerated up-dosing
4. To evaluate safety based on physician global assessment of disease activity

Primary Efficacy Endpoint: The primary clinical efficacy endpoint is the proportion of subjects who tolerate at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at the exit DBPCFC

Secondary Endpoints:

1. Change from baseline in tolerated dose of peanut protein at DBPCFC
2. Maximum dose achieved with no or mild symptoms at exit DBPCFC
3. Physician global assessment: Disease activity as measured on a 100 mm visual analogue scale (VAS)
4. Changes in peanut-specific IgE and IgG4, changes in skin prick test (SPT) mean wheal diameters
5. The safety of peanut OIT based on dosing symptoms and reported adverse events (AEs) including serious adverse events (SAEs)

6.3.2 Study Design

ARC001 was a phase 2, randomized, double-blind, placebo-controlled, multicenter safety study conducted at 8 sites located in the US. Peanut allergic subjects 4 to 26 years of age (N=56) were randomized (1:1) to Palforzia or placebo. Demographics were balanced between the treatment groups and comparable to the demographics in ARC003; most subjects were white, male, 4 to 11 years of age, and had other atopic conditions including allergic rhinitis and atopic dermatitis, and food allergy other than peanut. Slightly less than half had a history of asthma. These conditions were balanced between treatment groups with negligible variations attributable to the small sample size in ARC001.

Eligibility criteria included an entry DBPCFC (as in ARC003, subjects were required to have dose limiting symptoms to ≤100mg peanut protein). Subjects with severe or uncontrolled asthma were excluded as were subjects with a history of eosinophilic GI disease. After enrollment and randomization, subjects underwent initial dose escalation and up-dosing to 300mg Palforzia. Subjects continued 300mg Palforzia for two weeks before the study end and then underwent an exit DBPCFC.

The primary clinical efficacy endpoint was the proportion of subjects in each group who tolerated at least 300 mg of peanut protein with no more than mild symptoms at the exit DBPCFC. The study met its primary endpoint which was a higher response rate in Palforzia recipients compared to placebo in the ITT population using a two-sided test with a Type 1 error rate of 0.05. In the Palforzia group, 79% (95%CI: 60, 92) of subjects met the primary endpoint compared to 19% (95%CI: 7, 39) in the placebo group ($p<0.0001$).

Clinical Reviewer comment: Given the high placebo responder rate for the primary endpoint using 300mg peanut protein, the applicant chose to use a single dose of

600mg peanut protein at the exit DBPCFC as the primary endpoint in study ARC003 because a post hoc analysis of the 600mg dose in ARC001 demonstrated that fewer placebo recipients responded (0%, 95%CI: 0,13) compared to Palforzia recipients (62%, 95%CI: 42, 79).

In terms of safety, the most common AEs were GI-related. All 6 subjects who discontinued the study in the Palforzia group (at the 6mg or 12 mg dose level within approximately 4 weeks) reported gastrointestinal-related adverse events. One placebo subject discontinued (withdrawal of consent). One Palforzia treated subject had a systemic allergic reaction. This episode required epinephrine due to the study treatment (outside of epinephrine given in the oral food challenges). This episode occurred while the subject was exercising approximately 16 hours after the subject's last dose of study product. There was no known accidental ingestion of peanut. One Palforzia treated subject developed biopsy-proven eosinophilic esophagitis (EoE). No deaths occurred.

Clinical Reviewer comment: ARC001, as a phase 2 study, served to inform the initial safety profile of Palforzia and inform the study design of subsequent phase 3 studies. ARC001 will not be discussed further in this review.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety evaluations included collection of adverse reactions through diary cards and the collection of adverse events by direct inquiry by study staff, SAEs, and deaths. All summaries of adverse events were based on the safety population defined as all randomized subjects who received at least one dose of the assigned study treatment.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety of Palforzia was evaluated in 7 clinical studies submitted to the BLA. These studies were conducted in both North America and Europe. Safety data from four Phase 3 studies are summarized in this Section (ARC003, ARC0004, ARC007, and ARC011). Each of these studies evaluated the final doses and formulation in the age group (children 4 to 17 years of age) for which the applicant seeks licensure. Two Phase 2 studies, ARC001 and ARC002, were not included in the pooled summary of safety because of differences in how hypersensitivity data was collected. Data from these studies were reviewed and raised no additional safety concerns. ARC008 was not included in this section because this study contains blinded safety data.

To assess the overall safety profile of Palforzia in the age group intended for use, a pool of subjects 4 to 17 years of age from controlled (ARC003 and ARC007) and uncontrolled studies (ARC004 and ARC011) was analyzed. This dataset is presented in two groups: the controlled safety population and the integrated safety population. The controlled safety population consists of subjects who received Palforzia or placebo in the controlled studies. The integrated safety population is comprised of any subject who received at least one dose of Palforzia in both controlled and uncontrolled studies.

The information contained in the integrated summary of safety include data with a cut-off date of July 15, 2018. A safety update for on-going clinical studies (ARC004 and ARC011) was submitted to the BLA in amendment 7 with a cut-off date of December 21, 2018 which provides data for 5 additional months. These data were reviewed and are incorporated throughout Section 8.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

A total of 812 subjects were exposed to Palforzia in the 4 studies (ARC003, ARC004, ARC007, and ARC011) comprising the integrated safety population. Most of these subjects were white (76%) and male (60.7%). In the integrated safety population, most subjects had a history of food allergy other than peanut (65.4%) and also had other atopic conditions including asthma (51.5%), atopic dermatitis (60.0%), and allergic rhinitis (74.1%). These demographics mirror the controlled safety population because participants in the follow-on studies were recruited directly from the original phase 3 studies (ARC003 and ARC007). In the integrated safety population, subjects were treated with Palforzia for a median of 2 days during the initial dose escalation, 154 days during up-dosing, and 175 days during maintenance treatment.

The controlled safety population includes 709 subjects treated with Palforzia and 292 subjects treated with placebo from the combined populations of controlled studies ARC003 and ARC007. The study demographics in the controlled population are analogous to the integrated safety population and are balanced across treatment groups. In the controlled population the median treatment range was 155 days during initial dose escalation and up-dosing in the Palforzia group compared with 150 days for the placebo group. Subjects in the Palforzia group were treated on the maintenance dose of 300mg daily for a median of 175 days. For the placebo group, the median number of days on maintenance was 176 days.

Table 24, below, summarizes the demographic characteristics of the integrated safety population in subjects 4 to 17 years of age.

Table 24: Demographic Characteristics of Subjects 4 to 17 Years of Age in the Integrated Safety Population: Studies ARC003, ARC004, ARC007, and ARC011

	Palforzia N(%) Controlled Studies	**Placebo N(%) Controlled Studies**	**Total N(%) Integrated Population**
Number of subjects	709	292	812
Gender:	--	--	--
Male	426 (65.4)	178 (61.0)	493 (60.7)
Female	283 (39.9)	114 (39.0)	319 (39.3)
Age (years):	--	--	--
4 to 11	464 (65.4)	203 (69.5)	533 (65.6)
12 to 17	245 (34.6)	89 (30.5)	276 (34.0)
18 to 55[1]	0	0	3 (0.4)
Race	--	--	--
White	537 (75.7)	210 (71.9)	617 (76.0)
Black or African American	17 (2.4)	7 (2.4)	20 (2.5)
Asian	80 (11.3)	33 (11.3)	86 (10.6)

	Palforzia N(%) Controlled Studies	Placebo N(%) Controlled Studies	Total N(%) Integrated Population
American Indian or Alaska Native	1 (0.1)	1 (0.3)	1 (0.1)
Native Hawaiian or Other Pacific Islander	3 (0.4)	0	3 (0.4)
Multiple[2]	33 (4.7)	11 (3.8)	33 (4.1)
Other	38 (5.4)	30 (10.3)	52(6.4)
Ethnic origin	--	--	--
Hispanic or Latino	48 (6.8)	23 (7.9)	60 (7.4)
Not Hispanic or Latino	661 (93.2)	268 (91.8)	752 (92.6)
Geographic Region	--	--	--
North America	639 (90.1)	268 (91.8)	723 (89.0)
Europe	70 (9.9)	24 (8.2)	89 (11.0)
History of Asthma	--	--	--
Yes	373 (52.6)	142 (48.6)	418 (51.5)
No	336 (47.4)	150 (51.4)	394 (48.5)

Adapted from 125696/0: Summary of Clinical Safety, Table 7
[1] Includes subjects who turned 18 years of age prior to enrollment in ARC004
[2] Subjects in ARC007 were able to self-identify as multiracial and could select multiple categories

8.2.3 Categorization of Adverse Events

Please see section 6.1.12.1 for a description of how AEs were categorized in the study program as events in the four studies comprising the pooled safety database followed the approach in ARC003.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

The phase 3 studies ARC003 and ARC007 provided the majority of controlled data reviewed in the ISS and were included in two pools of safety data (controlled safety population and the integrated safety population) as described in Section 8.2. The remaining studies included in this section were open-label follow-on studies. Data from these studies are included in the integrated safety population as described in Section 8.2. The duration of follow up varied across pooled studies because some studies did not include a maintenance phase (ARC007) or up-dosing phase (ARC011). Randomization ratios differed between ARC003 (3:1) and ARC007 (2:1) in the treatment to placebo groups. In addition, all of the pooled data in Section 8 unless otherwise noted include subjects 4 through 17 years of age. Study ARC003 also included a small number of adult subjects 18 through 55 years of age.

Clinical Reviewer comment: Study ARC003 may have contributed more sensitive subjects (due to the entry OFC requirement) than ARC007 to the safety database. This is acceptable because it is a conservative analysis of the drug's reactogenicity; less sensitive patients who take Palforzia may experience fewer allergic adverse events. In addition, the exclusion of adult data is unlikely to affect clinical safety conclusions given the small number of adult participants and the similar trends in terms of systemic allergic reactions and epinephrine use as the pediatric participants.

8.4 Safety Results

A table summarizing adverse events, severe adverse events, and SAEs in subjects who received Palforzia in the controlled and integrated safety populations is below.

Table 25: Summary of Adverse Events Controlled Safety Population and the Integrated Safety Population by Dosing Period

	Palforzia Recipients in Controlled Studies N (%)	**Placebo Recipients in Controlled Studies N (%)**	**Palforzia Recipients in Total Integrated Population N (%)**
Initial Dose Escalation:	--	--	--
Total Subjects in population	709	292	812
Subjects with one or more adverse event	376 (53.0)	93 (31.8)	419 (51.6)
Severity of adverse event:	--	--	--
Mild	340 (48.0)	87 (29.8)	374 (46.1)
Moderate	36 (5.1)	6 (2.1)	44 (5.4)
Severe	0	0	1 (0.1)
Adverse events leading to study product discontinuation	13 (1.8)	3 (1.0)	15 (1.8)
Adverse events related to study product	336 (47.4)	68 (23.3)	373 (45.9)
Subjects with at least one serious adverse event	0	0	0
Serious adverse events related to study product	0	0	0
Adverse events related to:	--	--	--
Anaphylaxis/Systemic allergic reaction	5 (0.7)	1 (0.3)	5 (0.6)
Allergic reaction	344 (48.5)	76 (26.0)	382 (47.0)
Accidental food allergen exposure	1 (0.1)	2 (0.7)	2 (0.2)
Up-Dosing			
Total Subjects in population	693	289	794
Subjects with one or more adverse event	676 (97.5)	264 (91.3)	769 (96.9)
Severity of adverse event	--	--	--
Mild	319 (46.0)	178 (61.6)	364 (45.8)
Moderate	336 (48.5)	81 (28.0)	382 (48.1)
Severe	20 (2.9)	4 (1.4)	22 (2.8)
Adverse events leading to study product discontinuation	67 (9.7)	4 (1.4)	73 (9.2)
Adverse events related to study product	599 (86.4)	143 (49.5)	678 (85.4)
Subjects with at least one serious adverse event	6 (0.9)	2 (0.7)	6 (0.8)
Serious adverse events related to study product	3 (0.4)	0	3 (0.4)
Adverse events related to:	--	--	--
Anaphylaxis/Systemic allergic reaction	63 (9.1)	10 (3.5)	71 (8.9)
Allergic reaction	589 (85.0)	181 (62.6)	668 (84.1)
Accidental food allergen exposure	80 (11.5)	55 (19.0)	95 (12.0)
Maintenance	--	--	--
Total Subjects in population	310	118	661
Subjects with one or more adverse event	270 (87.1)	94 (79.7)	541 (81.8)
Severity of adverse event	--	--	--
Mild	161 (51.9)	57 (48.3)	344 (52.0)
Moderate	101 (32.6)	37 (31.4)	183 (27.7)

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Palforzia Recipients in Total Integrated Population N (%)
Severe	8 (2.6)	0	14 (2.1)
Adverse events leading to study product discontinuation	4 (1.3)	0	7 (1.1)
Adverse events related to study product	159 (51.3)	26 (22.0)	352 (53.3)
Subjects with at least one serious adverse event	4 (1.3)	1 (0.8)	8 (1.2)
Serious adverse events related to study product	1 (0.3)	0	2 (0.3)
Adverse events related to:	--	--	--
Anaphylaxis/Systemic allergic reaction	27 (8.7)	2 (1.7)	57 (8.6)
Allergic reaction	169 (54.5)	48 (40.7)	386 (58.4)
Accidental food allergen exposure	28 (9.0)	24 (20.3)	56 (8.5)
Overall	--	--	--
Total Subjects in population	709	292	812
Subjects with one or more adverse event	701 (98.9)	277 (94.9)	802 (98.8)
Severity of adverse event	--	--	--
Mild	305 (43.0)	173 (59.2)	321 (39.5)
Moderate	368 (51.9)	99 (33.9)	444 (54.7)
Severe	27 (3.8)	4 (1.4)	36 (4.4)
Adverse events leading to study product discontinuation	84 (11.8)	7 (2.4)	94 (11.6)
Adverse events related to study product	632 (89.1)	168 (57.5)	729 (89.8)
Subjects with at least one serious adverse event	10 (1.4)	3 (1.0)	13 (1.6)
Serious adverse events related to study product	4 (0.6)	0	5 (0.6)
Adverse events related to:	--	--	--
Anaphylaxis/Systemic allergic reaction	88 (12.4)	13 (4.5)	119 (14.7)
Allergic reaction	634 (89.4)	209 (71.6)	737 (90.8)
Accidental food allergen exposure	99 (14.0)	71 (24.3)	137 (16.9)

Adapted from 125696/0: Summary of Clinical Safety, Table 10, Table 11, Table 14.3.1.1.1, and Table 14.3.1.1.2

<u>Clinical Reviewer comment</u>: In the controlled and integrated safety population, most adverse events were mild to moderate in severity and decreased in frequency over time. In subjects who received a maintenance dose of 300mg Palforzia these events decreased in frequency the longer subjects took the maintenance dose of 300mg daily. In the integrated safety population, subjects who took Palforzia for 0 to13 weeks experienced more AEs (472/661 (71.9%)) compared to those who took the maintenance dose for 14 to 26 weeks (316/483 (65.4%)), 27to 52 weeks (178/284 (62.7%)), and >52 weeks (95/178 (53.4%)). In the same population, reports of allergic reactions decreased over time (0-13 weeks (309/661 (46.7%) compared to those who took the maintenance dose for 14-26 weeks (171/483 (35.4%), 27-52 weeks 95/284 (33.5%), and >52 weeks (39/178 (21.9%)). These data suggest the severity of allergic reactions diminish over time for subjects who are able to continue on a maintenance dose of Palforzia; however,

it is unclear whether the number of subjects who dropped out prior to the maintenance period may have contributed to this result. Data from study ARC003 (see Section 6.1.12.5) indicate that subjects in the ITT compared to the completer population (comprised of those who completed the peanut portion of the exit DBPCFC) reported increased systemic allergic reactions during up-dosing and maintenance, suggesting that those who dropped out or did not complete the exit DBPCFC were less tolerant to the study treatment.

In the controlled safety population, placebo recipients reported an increased number of adverse events related to accidental food exposure during maintenance compared to Palforzia recipients (9.0% for those on the maintenance dose of Palforzia versus 20.3% of placebo participants). In these subjects, 3.5% (Palforzia recipients) versus 5.1% (placebo group) of accidental food exposures were reported to be related to peanut exposure. These data suggest that Palforzia mitigates the risk of allergic reactions due to accidental ingestion of peanut-containing foods even when the culprit allergen is not identifiable.

Of note, the information contained in the integrated summary of safety included data with a cut-off date of July 15, 2018. A safety update for on-going clinical studies (ARC004 and ARC011) was submitted to the BLA in amendment 7 with a cut-off date of December 21, 2018 that provides data for 5 additional months. No new imbalances were noted in the safety update; the safety information is consistent with original submission.

8.4.1 Deaths

One death occurred in the safety population from study ARC007. This subject, from the placebo group, suffered a fatal injury related to a motor vehicle accident. This incident was considered not related to the study product.

Clinical Reviewer comment: This reviewer concurs with the applicant and the investigator assessment that this fatal SAE was not Palforzia related.

8.4.2 Nonfatal Serious Adverse Events

Thirteen serious adverse events (SAEs) occurred in the safety population. In the controlled safety population (studies ARC003 and ARC007) SAEs were reported by 10/709 (1.4%) Palforzia recipients: 6 subjects (0.9%) during up-dosing and 4 subjects (1.3%) during maintenance, respectively. Three placebo recipients reported SAEs (1.0%): 2 subjects (0.7%) during up-dosing and 1 subject (0.8%) during maintenance, respectively. Of these, 4 SAEs in Palforzia recipients were related to the study product: 3 anaphylactic reactions (2 during up-dosing, 1 during maintenance) and 1 asthma exacerbation during up-dosing. Two of 3 subjects who reported anaphylaxis SAEs discontinued from the study product. No SAEs in placebo recipients were considered related to the study product. The SAEs assessed as unrelated by the investigator in Palforzia recipients were mycoplasma pneumonia (1), asthma (1), gastroenteritis (1), streptococcal pharyngitis (1), concussion (1), and acute lymphocytic leukemia (1). In placebo recipients unrelated SAEs were appendicitis, humerus fracture, and craniocerebral injury. One death occurred in study ARC007. This subject, from the placebo group, suffered a fatal craniocerebral injury related to a motor vehicle accident.

In the integrated safety population, all of whom received at least one dose of Palforzia, (studies ARC003, ARC004, ARC007, and ARC011), 4 additional subjects experienced SAEs during maintenance in the follow-on studies. One systemic allergic reaction was considered related to the study product. This subject continued after a temporary dose interruption. The 3 unrelated SAEs were abdominal pain, dehydration, and streptococcal infection.

Clinical Reviewer comment: This reviewer agrees with the relatedness assessment of the SAEs described above to the product. In particular, this reviewer agrees that one of the SAEs of asthma is unrelated as it occurred in the context of a viral upper respiratory illness (URI). The unrelated episode of asthma occurred in a 5 year old female undergoing up-dosing on 3mg Palforzia who developed URI with subsequent viral testing positive for rhinovirus. No signs or symptoms were suggestive of a systemic allergic reaction. Palforzia was temporarily withheld. The subject was ultimately able to complete the course of Palforzia and ingested a maximum dose of 1000mg peanut protein with no more than mild symptoms during the exit DBPCFC.

The overall rate of SAEs was low and comparable between treatment and placebo groups (1.4% vs. 1.0%, respectively), however, more Palforzia recipients compared to placebo experienced SAEs of a systemic allergic reaction in the controlled safety population compared to placebo. This is expected as Palforzia recipients are being exposed to peanut protein daily in these studies. Similarly, the evaluation of systemic allergic reactions overall (those that were not SAEs) also demonstrates an imbalance between Palforzia and placebo recipients, with Palforzia recipients reporting more systemic reactions throughout the 3 study periods. See Section 8.4.8 for further discussion of systemic allergic reactions and epinephrine use as a rescue medication.

8.4.3 Study Dropouts/Discontinuations

In the controlled population, 22.2% of subjects taking Palforzia discontinued compared to 6.8% of the placebo group. The most common reasons in the Palforzia group were adverse event (9.6%) or withdrawal of consent (6.9%). Of the subjects who participated in the controlled studies (ARC003 and ARC007), 65.9% went on to participate in the follow-on studies (ARC004 and ARC011). In the integrated safety population, 26.5% of subjects treated with Palforzia dropped out. See Table 26 below.

Table 26: Subject Disposition for the Controlled Safety Population and the Integrated Safety Population by Dosing Period in Subjects 4 to 17 Years of Age

Disposition	**Palforzia Recipients in Controlled Studies N (%)**	**Placebo Recipients in Controlled Studies N (%)**	**Palforzia Recipients in Total Integrated Population N (%)**
Number randomized	712	293	812
Number in safety population[1]	709 (99.6)	292 (99.7)	812 (100.0)
Completed initial placebo-controlled study[2]	--	--	--
Yes	554 (77.8)	273 (93.2)	657 (80.9)

Disposition	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Palforzia Recipients in Total Integrated Population N (%)
No	158 (22.2)	20 (6.8)	155 (19.1)
Study period participation	--	--	--
Initial Dose Escalation	709 (99.6)	292 (99.7)	812 (100.0)
Up-dosing	693 (97.3)	289 (98.6)	794 (97.8)
Maintenance	575 (80.8)	276 (94.2)	661 (81.4)
Entered follow-on study	---	---	535 (65.9)
Completed follow-on study	---	---	
Yes	---	---	130 (16.0)
No	---	---	60 (7.4)
On-going	---	---	345 (42.5)
Discontinued	**158 (22.2)**	**20 (6.8)**	**215 (26.5)**
Adverse event	68 (9.6)	4 (1.4)	75 (9.2)
Dosing symptom	17 (2.4)	3 (1.0)	26 (3.2)
Withdrew consent	49 (6.9)	9 (3.1)	79 (9.7)
Protocol violation	1 (0.1)	0	3 (0.4)
Investigator decision	3 (0.4)	0	4 (0.5)
Sponsor decision	8 (1.1)	0	9 (1.1)
Death	0	1 (0.3)	0
Lost to follow-up	0	1 (0.3)	2 (0.2)
Other	12 (1.7)	2 (0.7)	17 (2.1)

Adapted from 125696/0: Summary of Clinical Safety, Table 4
[1] Some subjects withdrew prior to initiating therapy in study ARC003; two subjects did not receive Palforzia; 1 withdrew consent, 1 was a randomization error. One subject in the placebo group withdrew consent
[2]Completed ARC003 or ARC007

Clinical Reviewer comment: Discontinuations were more common in Palforzia recipients. Adverse events and withdrawal of consent were the most common reasons given for study discontinuation. This is consistent with the discontinuation data from efficacy study, ARC003, and emphasizes that the reactogenicity of the product leads highly sensitive subjects to discontinue therapy.

Discontinuations Due to Adverse Events

In the controlled safety population, 1.8% of subjects in the Palforzia group and 1.0% of subjects in the placebo group discontinued the study product during initial dose escalation. During up-dosing 9.7% in the Palforzia group and 1.4% in the placebo group discontinued during up-dosing. During maintenance, 1.3% of subjects in the Palforzia group and none the of subjects in the placebo group discontinued the study product. The most common adverse events leading to discontinuation of the study product during initial dose escalation and up-dosing were gastrointestinal (GI) disorders including abdominal pain (3.5% Palforzia, 0.3% placebo), vomiting (2.7%, 0%), nausea (1.8%, 0%), and systemic allergic reaction, including anaphylaxis (1.6%, 0%). During maintenance, the most common reason was systemic allergic reaction in 0.6% of subjects in the Palforzia group (0% placebo).

In the integrated safety population, 1.8% of subjects discontinued during initial up-dosing, 9.2% during up-dosing, 1.1% during maintenance, and 11.6% overall. The most common reasons overall were abdominal pain (3.7%), vomiting (2.5%), nausea (1.7%), and systemic allergic reaction/anaphylaxis (1.7%).

Adverse events leading to discontinuation are summarized in the table below.

Table 27: Summary of Adverse Events in ≥2 Subjects Leading to Discontinuation of Study Product Pediatric Safety Population 4 to 17 Years of Age by Preferred Term: Controlled Safety Population

	Palforzia Recipients in Controlled Studies N (%)	**Placebo Recipients in Controlled Studies N (%)**	**Palforzia Recipients in Total Integrated Population N (%)**
Up-Dosing:	--	--	--
Total Subjects in population	693	289	794
Subjects with at least 1 adverse event	67 (9.7)	4 (1.4)	73 (9.2)
Abdominal pain	18 (2.6)	0	21 (2.6)
Vomiting	17 (2.5)	0	18 (2.3)
Nausea	10 (1.4)	0	11 (1.4)
Abdominal discomfort	6 (0.9)	0	6 (0.8)
Upper abdominal pain	6 (0.9)	0	6 (0.8)
Oral pruritus	3 (0.4)	0	3 (0.4)
Eosinophilic esophagitis	3 (0.4)	0	4 (0.5)
Gastroesophageal reflux disease	3 (0.4)	0	3 (0.4)
Retching	3 (0.4)	0	3 (0.4)
Salivary hypersecretion	2 (0.3)	0	2 (0.3)
Throat irritation	5 (0.7)	0	6 (0.8)
Throat tightness	3 (0.4)	1 (0.3)	3 (0.4)
Wheezing	3 (0.4)	1 (0.3)	3 (0.4)
Cough	3 (0.4)	0	3 (0.4)
Rhinorrhea	2 (0.3)	0	2 (0.3)
Systemic allergic reaction/anaphylaxis	9 (1.3)	0	9 (1.1)
Urticaria	5 (0.7)	0	5 (0.6)
Pruritus	2 (0.3)	0	2 (0.3)
Rash	2 (0.3)	0	2 (0.3)
Chest pain	2 (0.3)	0	2 (0.3)
Maintenance			
Total Subjects in population	310	118	661
Subjects with at least 1 adverse event	4 (1.3)	0	7 (1.1)
Abdominal pain	0	0	0
Vomiting	0	0	0
Nausea	0	0	0
Abdominal discomfort	0	0	0
Upper abdominal pain	0	0	0
Oral pruritus	0	0	0
Eosinophilic esophagitis	0	0	0
Gastroesophageal reflux	0	0	0
Retching	0	0	0
Salivary hypersecretion	0	0	0
Throat irritation	0	0	0
Throat tightness	0	0	1 (0.2)
Wheezing	1 (0.3)	0	1 (0.2)
Cough	0	0	0
Rhinorrhea	0	0	0
Systemic allergic reaction/anaphylaxis	2 (0.6)	0	3 (0.5)
Urticaria	0	0	1 (0.2)

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Palforzia Recipients in Total Integrated Population N (%)
Pruritus	0	0	0
Rash	0	0	0
Chest pain	0	0	0

Adapted from 125696/0 Summary of Clinical Safety Table 28, Table, 29, and Table 14.3.1.10.1

Clinical Reviewer comment: The majority of discontinuations in the controlled and integrated safety populations occurred during the up-dosing period in subjects taking Palforzia with the most common events for discontinuation being gastrointestinal adverse events and systemic allergic reactions. No concerning imbalance in discontinuations between treatment groups occurred during the short initial dose escalation period. Adverse events leading to study drug discontinuation occur early, in the up-dosing period; once subjects reach a maintenance dose of 300mg daily of Palforzia adverse events leading to discontinuation decrease in frequency compared to placebo recipients who maintained a strict peanut avoidance diet as per current clinical recommendations. It not yet clear if long-term Palforzia therapy will result in fewer AEs leading to discontinuation, such that the rate is comparable to the frequency of AEs reported by placebo recipients in controlled studies.

8.4.4 Common Adverse Events

Below are tables summarizing common adverse events by MedDRA Preferred Term for the controlled and integrated safety populations during Up-Dosing and Maintenance periods. These periods comprised the majority of the safety evaluation (the initial dose escalation lasted 2 days and is part of the up-dosing procedure) and are therefore representative of the safety events occurring in the controlled and integrated safety population. Adverse events were less frequent during the initial dose escalation which occurred over a 2-day period; however, similar common AEs were reported during initial dose escalation as those reported in the up-dosing and maintenance periods (data not shown).

The most common adverse events in the controlled safety population that were at least 5% higher in the Palforzia group compared to placebo were abdominal pain, throat irritation, pruritus, vomiting, cough, nausea, urticaria, upper abdominal pain, abdominal discomfort, oral pruritus, and sneezing. The frequency of these events decreased in the maintenance phase compared to the up-dosing phase. The frequency of these common adverse events was similar in the integrated safety population compared to Palforzia recipients in the controlled safety population throughout the 3 study periods.

Table 28: Summary of Common Adverse Events in at Least 5% in the Pediatric Safety Population 4 to 17 Years of Age by Preferred Term: Controlled Safety Population and Integrated Safety Population

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Palforzia Recipients in Total Integrated Population N (%)
Up-Dosing:	--	--	--

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Palforzia Recipients in Total Integrated Population N (%)
Total Subjects in population	693	289	812
Subjects with at least 1 adverse event	676 (97.5)	264 (91.3)	769 (96.9)
Abdominal pain	314 (45.3)	51 (17.6)	346 (43.6)
Throat irritation	279 (40.3)	49 (17.0)	303 (38.2)
Pruritus	225 (32.5)	59 (20.4)	240 (30.2)
Vomiting	253 (36.5)	47 (16.3)	282 (35.5)
Cough	221 (31.9)	68 (23.5)	259 (32.6)
Nausea	224 (32.3)	41 (14.2)	249 (31.4)
Urticaria	197 (28.4)	54 (18.7)	222 (28.0)
Upper abdominal pain	209 (30.2)	39 (13.5)	237 (29.8)
Abdominal discomfort	172 (24.8)	35 (12.1)	189 (23.8)
Oral pruritus	174 (25.1)	19 (6.6)	191 (24.1)
Sneezing	140 (20.2)	31 (10.7)	154 (19.4)
Throat tightness	98 (14.1)	8 (2.8)	109 (13.7)
Oral paresthesia	94 (13.6)	11 (3.8)	100 (12.6)
Wheezing	85 (12.3)	21 (7.3)	95 (12.0)
Anaphylactic reaction	63 (9.1)	10 (3.5)	71 (8.9)
Tongue pruritus	63 (9.1)	10 (3.5)	71 (8.9)
Lip pruritus	62 (8.9)	6 (2.1)	69 (8.7)
Dyspnea	53 (7.6)	5 (1.7)	62 (7.8)
Ear pruritus	41 (5.9)	2 (0.7)	42 (5.3)
Chest discomfort	37 (5.3)	2 (0.7)	41 (5.2)
Maintenance	--	--	--
Total Subjects in population	310	118	661
Subjects with at least 1 adverse event	270 (87.1)	94 (79.7)	541 (81.8)
Abdominal pain	46 (14.8)	7 (5.9)	92 (13.9)
Throat irritation	43 (13.9)	11 (9.3)	105 (15.9)
Pruritus	45 (14.5)	14 (11.9)	90 (13.6)
Vomiting	50 (16.1)	14 (11.9)	107 (16.2)
Cough	61 (19.7)	22 (18.6)	129 (19.5)
Nausea	45 (14.5)	8 (6.8)	89 (13.5)
Urticaria	63 (20.3)	17 (14.4)	128 (19.4)
Upper abdominal pain	41 (13.2)	9 (7.6)	70 (10.6)
Abdominal discomfort	19 (6.1)	7 (5.9)	68 (10.3)
Oral pruritus	39 (12.6)	5 (4.2)	60 (9.1)
Sneezing	33 (10.6)	5 (4.2)	51 (7.7)
Throat tightness	20 (6.5%)	0	31 (4.7)
Oral paresthesia	23 (7.4)	2 (1.7)	33 (5.0)
Wheezing	19 (6.1)	10 (8.5)	39 (5.9)
Anaphylactic reaction	27 (8.7)	2 (1.7)	57 (8.6)
Tongue pruritus	10 (3.2)	1 (0.8)	24 (3.6)
Lip pruritus	12 (3.9)	1 (0.8)	30 (4.5)
Dyspnea	17 (5.5)	1 (0.8)	38 (5.7)
Ear pruritus	7 (2.3)	0	12 (1.8)
Chest discomfort	8 (2.6)	0	17 (2.6)

Adapted from 125696/0 Summary of Clinical Safety Table 14, Table 15, Table 14.3.1.2.1

<u>Clinical Reviewer comment</u>: During initial dose escalation the rates of common adverse events were lower overall compared to up-dosing and maintenance. As in up-dosing and maintenance, the incidence of adverse events was higher in the Palforzia group (53.0%)

compared to the placebo group (31.8%). No concerning differences in the incidence of common adverse events were noted between the initial dose escalation compared to the up-dosing and maintenance periods in the Palforzia treated subjects. The lower incidence of adverse events during initial dose escalation is likely due to the small amount of peanut protein ingested (0.5 to 6mg) and short duration of the initial dose escalation period (2 days). The most frequently reported AEs consisted of gastrointestinal complaints (abdominal pain, throat irritation, pruritus, vomiting, nausea, upper abdominal pain, and abdominal discomfort) and led to study discontinuation in Palforzia recipients. The incidence of GI-related AEs is anticipated given the oral route of exposure. Though study discontinuations were high, 80% of recipients tolerated the therapy to reach the maintenance period.

8.4.5 Clinical Test Results

Not applicable.

8.4.6 Systemic Adverse Events

Please see Section 8.4.8

8.4.7 Local Reactogenicity

Not applicable.

8.4.8 Adverse Events of Special Interest

Select adverse events of special interest (AESIs) specific to oral immunotherapy as a treatment for IgE-mediated food allergy were identified through literature review of published studies. These events included systemic allergic reactions and anaphylaxis, use of epinephrine to treat allergic reactions, and eosinophilic esophagitis. A summary and discussion of the AESIs occurring in this study program are presented below.

Systemic Allergic Reactions and Anaphylaxis

In the controlled population, 9.4% of Palforzia recipients reported systemic allergic reactions during initial dose escalation and up-dosing combined compared to 3.8% of placebo recipients. Most subjects reported one episode of a systemic allergic reaction. In the Palforzia group,1.6% discontinued due to systemic allergic reactions versus no subjects in the placebo group during initial dose escalation and up-dosing. During maintenance, 8.7% of Palforzia recipients and 1.7% of placebo recipients reported systemic allergic reactions; 0.6% of subjects taking Palforzia and no subjects in the placebo group discontinued due to systemic allergic reaction. Three subjects in the Palforzia group had a serious systemic allergic reaction, including 2 (0.3%) during up-dosing and 1 (0.3%) during maintenance treatment with Palforzia. During initial dose escalation and up-dosing combined, 6.1% in the Palforzia group and 3.1% placebo had a systemic allergic reaction that required epinephrine use. Most of the epinephrine was administered outside of the clinic facilities.

While ARC007 did not require an entry food challenge, the frequency of patient history of systemic allergic reaction to peanut was similar in the study population to those in ARC003, which required an entry food challenge. In ARC003 72.1% of participants

reported a history of 1 or more systemic allergic reactions to peanut while in study ARC007 60% of participants reported a history of 1 or more systemic allergic reactions to peanut though most (85.7%) reported using epinephrine, antihistamines, or other medications to treat a qualifying (see Section 6.2.2) allergic reaction to peanut. In ARC003, 14.2% of Palforzia recipients reported systemic allergic reactions vs. 3% of placebo recipients. During study ARC007 10.7% of Palforzia recipients vs. 5.4% of placebo recipients reported a systemic allergic reaction.

Occurrence of systemic allergic reactions related to subject-reported accidental food exposures decreased from up-dosing (9 events in Palforzia recipients and 9 events in placebo recipients) to maintenance (3 events in Palforzia recipients and 1 event in placebo recipients). Similarly, occurrence of all adverse events related to subject-reported accidental food allergen exposures decreased from 11.5% of subjects during up-dosing to 9.0% during maintenance in Palforzia recipients. In placebo recipients, occurrence of these adverse events did not change from up-dosing (19.0%) to maintenance (20.3%). During maintenance dosing, 3.5% of accidental food exposures in Palforzia recipients versus 5.1% in placebo recipients were reported to be related to peanut exposure (data not shown). As outlined in Table 29, none of these accidental exposures were due to unknown food allergens; however, subjects may not have been able to identify peanut as a clear trigger in some cases due to food contamination with small amounts of peanut protein.

A similar proportion of subjects reported systemic allergic reactions in the integrated safety population. Occurrence of systemic allergic reactions decreased over time when evaluating subjects on the maintenance dosing schedule. Six systemic allergic reactions were reported in subjects who took a maintenance dose of Palforzia >52 weeks compared with 20 episodes at 27 to 52 weeks, 21 episodes at 14 to 26 weeks, and 32 episodes at 0 to 13 weeks.

Extrinsic Cofactor Analysis
An analysis of the most common (at least 10% of subjects in either group) extrinsic co-factors that may have contributed to systemic allergic reactions in the pediatric controlled safety population are as follows: Exercise (40.4% Palforzia, 7.7% placebo), exposure to hot water (13.5%, 0%), intercurrent illness (12.4%, 0%), fasting (11.2%, 0%), and other (14.6%, 7.7%). Two (2.2%) Palforzia-treated subjects reported uncontrolled asthma, 5 (5.6%) Palforzia-treated subjects reported menstruation as a co-factor, and 3 (3.4%) Palforzia-treated subjects reported NSAID use a co-factor. No placebo subjects reported intercurrent illness or NSAID use as a co-factor while one reported menstruation. Among the 5 Palforzia recipients who reported anaphylaxis (i.e., a severe systemic allergic reaction), co-factors included exercise (3 subjects), exercise and fasting (1), or no cofactors (1). Three subjects reported serious systemic allergic reactions. Co-factors influencing these episodes were intercurrent illness (2) and no co-factors (1).

Table 29: Summary of Systemic Allergic and Anaphylactic Reactions in the Controlled and Integrated Safety Population 4 to 17 Years of Age

	Palforzia Recipients in Controlled Studies N (%)	**Placebo Recipients in Controlled Studies N (%)**	**Palforzia Recipients in Total Integrated Population N (%)**
Initial Dose Escalation:	--	--	--

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Palforzia Recipients in Total Integrated Population N (%)
Total subjects in population	709	292	812
Number of systemic allergic reactions	5	1	5
Number of systemic allergic reactions by trigger	--	--	--
Study product	5	0	5
Food allergen	0	1	0
Non-food allergen	0	0	0
Unknown	0	0	0
Number of subjects with systemic allergic reactions	--	--	--
1 episode	5 (0.7)	1 (0.3)	5 (0.6)
2 episodes	0	0	0
≥ 3 episodes	0	0	0
Severity of systemic allergic reaction[1]	--	--	--
Mild	5 (0.7)	1 (0.3)	5 (0.6)
Moderate	0	0	0
Severe (anaphylaxis)	0	0	0
Considered serious adverse event	0	0	0
Used epinephrine to treat reaction	3 (0.4)	1 (0.3)	3 (0.4)
Location of reaction			
Other than study site[2]	0	1(0.3)	0
Study site	3 (0.4)	0	3 (0.4)
Up-Dosing:			
Total subjects in population	693	289	794
Number of systemic allergic reactions	76	10	85
Number of systemic allergic reactions by trigger	--	--	--
Study product	63	1	68
Food allergen	8	9	12
Non-food allergen	5	0	5
Unknown	0	0	0
Number of subjects with systemic allergic reactions	--	--	--
1 episode	50 (7.2)	10 (3.5)	57 (7.2)
2 episodes	13 (1.9)	0	14 (1.8)
≥ 3 episodes	0	0	0
Severity of systemic allergic reactions[1]	--	--	--
Mild	24 (3.5)	4 (1.4)	28 (3.5)
Moderate	35 (5.1)	6 (2.1)	38 (4.8)
Severe (anaphylaxis)	4 (0.6)	0	5 (0.6)
Considered serious adverse event	2 (0.3)	0	2 (0.3)
Used epinephrine to treat reaction	41 (5.9)	8 (2.8)	47 (5.9)
Location of reaction	--	--	--
Home	33 (4.8)	7 (2.4)	38 (4.8)
Study site	11 (1.6)	1 (0.3)	13 (1.6)
Maintenance			
Total subjects in population	310	118	661
Number of systemic allergic reactions	33	2	79

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Palforzia Recipients in Total Integrated Population N (%)
Number of systemic allergic reactions by trigger	--	--	--
Study product	28	1	66
Food allergen	4	1	11
Non-food allergen	1	0	2
Unknown	0	0	0
Number of subjects with systemic allergic reactions	--	--	--
1 episode	23 (7.4)	2 (1.7)	46 (70)
2 episodes	2 (0.6)	0	3 (0.5)
≥ 3 episodes	2 (0.6)	0	7 (1.1)
Severity of systemic allergic reactions[1]	--	--	--
Mild	12 (3.9)	0	25 (3.8)
Moderate	14 (4.5)	2 (1.7)	26 (3.9)
Severe (anaphylaxis)	1 (0.3)	0	5 (0.8)
Considered serious adverse event	1 (0.3)	0	2 (0.3)
Used epinephrine to treat reaction	19 (6.1)	2 (1.7)	43 (6.5)
Location of reaction			
Other than study site	18 (5.8)	1 (0.8)	40 (6.1)
Study site	2 (0.6)	1 (0.8)	4 (0.6)

Adapted from 125696/0 Summary of Clinical Safety Table 31, Table 33, Table 14.3.7.4.1, Table 14.3.7.4.2
N = number of subjects
[1] Anaphylaxis graded by severity by European Academy of Allergy and Clinical Immunology (EAACI) grading scale
[2] Administration of study product was done entirely in clinic during the initial dose escalation period

Clinical Reviewer comment: The differences in reports of systemic allergic reactions between controlled studies ARC003 and ARC007 are small; no conclusion can be made when comparing systemic allergic reactions between the studies. Overall, Palforzia treated subjects reported more systemic reactions than placebo recipients in the controlled study population. Most of these reactions were graded as mild to moderate; however, it is important to note that most patients who have a history of IgE-mediated food allergy are instructed to immediately treat any allergic symptom, whether mild, moderate, or severe, upon recognition before reactions progress to be life-threatening. Most reactions occurred at home or outside of the study site in Palforzia recipients compared to placebo. Subjects who received Palforzia also reported more reactions in the clinic than those who took the placebo treatment. Treatment with Palforzia increases the incidence of systemic reactions regardless of location (i.e., whether treatment is monitored in a healthcare setting or at home).

The incidence of systemic allergic reactions appears to decrease over time. Six systemic allergic reactions were reported in subjects who took a maintenance dose of Palforzia >52 weeks compared with those 20 episodes at 27 to 52 weeks, 21 episodes at 14 to 26 weeks, and 32 episodes at 0 to13 weeks in the integrated safety population as discussed above. As noted previously (see reviewer comment in Section 6.1.12.5), these data do not account for study drop-outs which may have contributed to the lower rates of reactions reported with longer treatment duration. Regardless, patients taking

Palforzia should continue to carry injectable epinephrine to treat systemic allergic reactions.

In addition, while not formally explored in the efficacy analysis, rates of allergic reactions related to subject-reported accidental food exposure support the efficacy findings demonstrating a Palforzia-related treatment benefit. In fact, these data may be more predictive than DBPCFC results of the real-world impact of Palforzia in preventing reactions due to accidental peanut exposure. However, the analysis is limited by the small number of events.

Use of Epinephrine

In the controlled safety population 10.4% of subjects in the Palforzia group and 4.8% in the placebo group had at least 1 episode of epinephrine use during initial dose escalation and up-dosing combined. During maintenance 7.7% of subjects in the Palforzia group 3.4% of subjects in the placebo group had at least 1 episode of epinephrine use. Of note, an episode was defined as the administration of 1 or more epinephrine doses within 2 hours. During initial dose escalation and up-dosing combined this accounted for 6.1% of the Palforzia group and 3.1% of the placebo group. During maintenance 6.1% of the Palforzia group versus 1.7% placebo group used epinephrine to treat systemic allergic reactions. All of the reactions requiring epinephrine during the initial dose escalation occurred at the study site. Approximately 70% of the reactions occurred at home during the up-dosing period, while approximately 90% occurred at home during the maintenance period.

Clinical Reviewer comment: This location breakdown of epinephrine use is expected given the Palforzia dosing procedures. It is notable that the imbalance between Palforzia and placebo treated subjects is maintained regardless of the location of the reaction (study site vs. home).

In the integrated safety population, 2.0% of subjects reported at least 1 episode of epinephrine use during initial dose escalation, 9.9% during up-dosing and 8.2% during maintenance. Most epinephrine use in the integrated safety population was for systemic allergic reaction.

Table 30: Summary of Use of Epinephrine as a Rescue Medication in the Controlled and Integrated Safety Population 4 to 17 Years of Age

	Palforzia Recipients in Controlled Studies N (%)	**Placebo Recipients in Controlled Studies N (%)**	**Palforzia Recipients in Total Integrated Population N (%)**
Initial Dose Escalation:	--	--	--
Total subjects in population	709	292	812
Subjects with any use of epinephrine	12 (1.7)	2 (0.7)	16 (2.0)
Age subcategory	--	--	--
4-11 years	7 (58.3)	2 (100.0)	10 (62.5)
12-17 years	5 (41.7)	0	6 (37.5)

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Palforzia Recipients in Total Integrated Population N (%)
Number of epinephrine doses per episode	--	--	--
1 dose	12 (100.0)	2 (100.0)	15 (93.8)
2 doses	0	0	1 (6.3)
≥3 doses	0	0	0
Severity of AE associated with the episode	--	--	--
Grade 1	8 (66.7)	1 (50.0)	9 (56.3)
Grade 2	4 (33.3)	1 (50.0)	6 (37.5)
Grade 3	0	0	1 (6.3)
Grade 4	0	0	0
Grade 5	0	0	0
Location of episode	--	--	--
Home	0	1 (50.0)	0
Study site	12 (100.0)	1 (50.0)	16 (100.0)
Up-Dosing:	--	--	--
Total subjects in population	693	289	794
Subjects with any use of epinephrine	67 (9.7)	12 (4.2)	79 (9.9)
Age subcategory	--	--	--
4-11 years	35 (52.2)	8 (66.7)	40 (50.6)
12-17 years	32 (47.8)	4 (33.3)	39 (49.4)
Number of epinephrine doses per episode	--	--	--
1 dose	72 (87.8)	11 (91.7)	86 (88.7)
2 doses	9 (11.0)	1 (8.3)	10 (10.3)
≥3 doses	1 (1.2)	0	1 (1.01)
Severity of AE associated with the episode[1]	--	--	--
Grade 1	29 (35.4)	5 (41.7)	33 (34.0)
Grade 2	44 (53.7)	7 (58.3)	53 (54.6)
Grade 3	7 (8.5)	0	8 (8.2)
Grade 4	0	0	0
Grade 5	0	0	0
Location of episode	--	--	--
Home	58 (70.7)	11 (91.7)	
Study site	24 (29.3)	1 (8.3)	
Maintenance	--	--	--
Total subjects in population	310	118	661
Subjects with any use of epinephrine	24 (7.7)	4 (3.4)	54 (8.2)
Age sub category	--	--	--
4-11 years	10 (41.7)	4 (100)	29 (53.7)
12-17 years	14 (58.3)	0	25 (46.3)
Number of epinephrine doses per episode	--	--	--
1 dose	27 (93.1)	4 (100.0)	70 (95.9)
2 doses	1 (3.4)	0	2 (2.7)
≥3 doses	1 (3.4)	0	1 (1.4)
Severity of AE associated with the episode	--	--	--
Grade 1	12 (41.4)	2 (50.0)	26 (35.6)

	Palforzia Recipients in Controlled Studies N (%)	Placebo Recipients in Controlled Studies N (%)	Palforzia Recipients in Total Integrated Population N (%)
Grade 2	16 (55.2)	2 (50.0)	43 (58.9)
Grade 3	1 (3.4)	0	4 (5.5)
Grade 4	0	0	0
Grade 5	0	0	0
Location of episode	--	--	--
Home	26 (89.7)	3 (75.0)	67 (91.8)
Study site	3 (10.3)	1 (25.0)	6 (8.2)

Adapted from 125696/0 Clinical Summary of Safety Table 34, Table 35, Table 14.3.7.3.1
The CoFAR severity grading scale (Table 14, Section 6.1.12.1) was used for coding allergic AEs
[1] Grading criteria is missing for 2 episodes occurring during up-dosing in the controlled safety population and for 3 episodes during up-dosing in the integrated safety population

Clinical Reviewer comment: More epinephrine use occurred during up-dosing compared to the maintenance period in Palforzia recipients compared to placebo. Overall, Palforzia recipients reported more epinephrine use compared to placebo for all dosing periods. With the exception of the initial dose escalation, most epinephrine was administered outside of the clinic though subjects treated with Palforzia demonstrated an increased requirement for epinephrine to treat allergic reactions in the clinic setting compared to those who received placebo. These data demonstrate that the simple peanut avoidance diet practiced by the placebo group results in fewer systemic allergic reactions and consequently less need for treatment with epinephrine. While oral food challenge results support the efficacy of Palforzia for decreasing the frequency and severity of systemic allergic reactions, including anaphylaxis, following accidental peanut exposure, Palforzia does not reduce the overall risk of systemic allergic reactions and subsequent epinephrine use in subjects with IgE-mediated peanut allergy; the Prescribing Information (PI) should reflect these risks to ensure prescribers and patients are aware of the limitations of Palforzia therapy.

Eosinophilic Esophagitis

In the controlled safety population, 3/693 (0.4%) Palforzia recipients developed biopsy confirmed eosinophilic esophagitis (EoE) during up-dosing. In the integrated safety population, 1 additional subject was diagnosed with EoE during up-dosing. Three of these episodes were considered on-going at the time of BLA submission. Another subject diagnosed with biopsy confirmed EoE in study ARC004 was reported in a safety update submitted to the BLA for on-going studies for a total of 5 cases in the integrated safety population. This episode was considered on-going. This case was considered not to be related because EoE was thought to be present prior to treatment with Palforzia. The subject had symptoms of constipation and stomach pain for which the subject took polyethylene glycol prior to beginning up-dosing with Palforzia in ARC004 (the subject was in the placebo group in ARC003). The frequency of EoE in subjects taking Palforzia is 0.6% (5/812) in the pediatric integrated safety population.

One subject in ARC001 was diagnosed with biopsy confirmed EoE one month after withdrawing from the study during the up-dosing phase at the 12mg dose due to vomiting (this case was considered on-going), one subject in ARC002 (a former placebo subject from ARC001) developed biopsy confirmed EoE during Palforzia treatment

(considered on-going), and one adult subject in ARC004 also developed biopsy confirmed EoE during maintenance dosing (this case was considered resolved but is not included in the cases for the pediatric integrated safety population because the subject is an adult). In addition, 4 reports of biopsy-confirmed EoE (all considered on-going) in Palforzia recipients occurred in ARC008. A total of 12 subjects in the clinical program have developed EoE. No subjects taking placebo were diagnosed with EoE in this clinical development program.

Clinical Reviewer comment: This reviewer agrees that interpretation of the EoE case reported in the subject in ARC004 who a placebo recipient in ARC003 was is confounded by pre-existing gastrointestinal symptoms that were not fully evaluated prior to enrollment in the trial. However, the potential for Palforzia to accelerate the subject's underlying disease process cannot be ruled out. Therefore, in contrast to the study investigator's assessment, this reviewer considers this case of EoE related to the study product.

Eosinophilic esophagitis is a known risk for patients with atopic disease, particularly those diagnosed with IgE-mediated food allergy. Patients with EoE are managed by topical (swallowed) corticosteroids, while some choose to undergo elimination diets meant to avoid common food allergens associated with EoE. The latter use of elimination diets is more typically followed in pediatric patients. EoE is a particular concern in subjects receiving oral immunotherapy (OIT) for IgE-mediated food allergy as OIT is hypothesized to trigger or worsen underlying EoE. The data from this program appear to support this hypothesis.

*While the incidence of EoE in both the controlled and integrated safety population is low (*3/693 *(0.4%) and 5/812 (0.6%), respectively) and generally occurred early in treatment (during up-dosing), only subjects exposed to Palforzia were with diagnosed EoE in this clinical development program. Therefore, patients taking Palforzia should be advised of this risk. Appropriately, the proposed Prescribing Information (PI) notes this risk and advises that patients who develop dysphagia, gastroesophageal reflux, chest pain, or abdominal pain should discontinue Palforzia and healthcare practitioners are advised to consider a diagnosis of EoE. This reviewer recommends that the Warnings and Precautions Statement in the USPI provide an estimate of this risk from the clinical development program as outlined in 21CFR201.57. Labeling negotiations regarding this latter point are ongoing with the applicant at the time of this review.*

The information contained in the integrated summary of safety contained data with a cut-off date of July 15, 2018. A safety update for on-going clinical studies (ARC004 and ARC011) was submitted to the BLA in amendment 7 that provides data with a cut-off date of December 21, 2018 for 5 additional months. One additional case of EoE was diagnosed during this time. A subject in ARC004 (who received placebo in ARC003) on maintenance therapy with Palforzia was diagnosed with biopsy-confirmed EoE and discontinued from the study. This case is discussed in above.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

A single maintenance dose was evaluated in this clinical development program. Please see Section 8.4.4 for a tabulation of common adverse events occurring during up-dosing and maintenance therapy.

8.5.2 Time Dependency for Adverse Events

In the controlled safety population, median time to onset for all adverse reactions was 5 minutes in Palforzia recipients and 30 minutes in placebo recipients during initial dose escalation and up-dosing combined. During maintenance, the median time to onset was 15 minutes in Palforzia recipients and 336 minutes in placebo recipients. For the most common adverse events with at least 5% higher incidence in Palforzia recipients over placebo, most subjects experienced these events within 30 minutes after dosing.

The median duration for all adverse reactions was 105 minutes in Palforzia recipients and 90 minutes in placebo recipients during initial dose escalation and up-dosing combined. During maintenance, the median duration was 104 minutes in Palforzia recipients and 120 minutes in placebo recipients.

Median times to onset and durations of adverse reactions were comparable in the integrated safety population.

Clinical Reviewer comment: The timing of onset and duration of adverse reactions and common adverse events (which are all allergic in nature) in Palforzia recipients is expected for events that are a result of exposure to peanut in subjects with IgE-mediated peanut hypersensitivity.

8.5.3 Product-Demographic Interactions

Not applicable.

8.5.4 Product-Disease Interactions

No association between sensitivity (or minimum reactive dose) on entry DBPCFC (for study ARC003) and reports of systemic allergic reactions, epinephrine use, study discontinuation due to adverse events or other reasons was seen in the data (data not shown, response to IR request July 17, 2019). No meaningful difference in adverse events was noted in subjects with asthma, allergic rhinitis, or atopic dermatitis. However, none of the studies were powered to demonstrate a statistically significant difference in adverse events between subgroups within the Palforzia and placebo groups.

As noted in Section 8.2.2, most study participants reported a clinical history of other atopic conditions including food allergy other than peanut, asthma, atopic dermatitis, and allergic rhinitis. Patients with clinical history of IgE-mediated food allergy and atopic dermatitis can experience increase in eczematous flares when exposed to a food allergen [9]. Based on the common AE data, treatment with Palforzia does not appear to increase reports of eczema in subjects with atopic dermatitis compared to those treated

with placebo in the controlled safety population (1.4% Palforzia versus 4.3% placebo during initial dose escalation and up-dosing combined; 0% Palforzia versus 2% placebo during maintenance).

Clinical Reviewer comment: Though this is a small sample size and the study was not designed to evaluate a clinical impact on atopic dermatitis symptoms, the data do not suggest Palforzia will lead to a flare of atopic dermatitis/eczema.

Given the increased risk of death from anaphylaxis in uncontrolled asthmatics compared to those without asthma, subgroup analysis of safety data in this population is particularly important and discussed in additional detail below.

Asthmatics

Subjects with uncontrolled or severe asthma were specifically excluded from study participation; however, asthma was a common co-morbidity with approximately half of the controlled study population reporting an asthma diagnosis. Respiratory-specific adverse events occurred more frequently in subjects with a history of asthma compared to those without asthma (Table 31 below). These events include asthma, wheezing, dyspnea and throat tightness. Palforzia-treated subjects with asthma reported increased incidence of dyspnea and throat tightness than subjects with asthma in the placebo group.

In the controlled safety population, among subjects with a history of asthma, systemic allergic reactions occurred more frequently in those taking Palforzia compared to placebo recipients (9.7% during up-dosing and 7.7% during maintenance in Palforzia recipients vs. 3.5% up-dosing and 1.6% maintenance in placebo recipients). In subjects with no history of asthma, Palforzia recipients reported more systemic allergic reactions (8.4% up-dosing and 9.7% maintenance) compared to placebo recipients (3.4% up-dosing and 1.8% maintenance). Further analysis shows subjects with a history of asthma taking Palforzia reported more moderate systemic allergic reactions (but not more mild or severe reactions) during up-dosing compared to subjects without asthma (6.1% vs 3.9%). Similar rates of mild, moderate, and severe systemic reactions occurred during maintenance in both subpopulations (data not shown). Epinephrine use was reported more frequently in asthmatic subjects taking Palforzia during up-dosing compared to those with no history of asthma (10.5% vs. 8.7%). During maintenance, this percentage was similar in asthmatics compared to non-asthmatics taking Palforzia (7.7% vs. 7.8%).

The Asthma Control Test (ACT) was administered for studies ARC003, ARC007, ARC004, and ARC011 at baseline and throughout the studies. No concerning change in subjects' asthma control was noted in subjects 4 to 11 years of age or 12 to 17 years of age (data not shown).

Table 31: Summary of Respiratory Adverse Events in the Pediatric Safety Population 4 to 17 Years of Age With and Without Asthma by Preferred Term: Controlled Safety Population

	Palforzia Recipients With Asthma in Controlled Studies N(%)	Placebo Recipients With Asthma in Controlled Studies N(%)	Palforzia Recipients Without Asthma in Controlled Studies N(%)	Placebo Recipients Without Asthma in Controlled Studies N(%)
Up-Dosing:	--	--	--	--
Total Subjects in population	361	141	332	148
Asthma	41 (11.4)	15 (10.6)	3 (0.9)	1 (0.7)
Cough	117 (32.4)	34 (24.1)	104 (31.3)	34 (23.0)
Wheezing	55 (15.2)	15 (10.6)	30 (9.0)	6 (4.1)
Dyspnea	40 (11.1)	4 (2.8)	13 (3.9)	1 (0.7)
Dysphonia	10 (2.8)	2 (1.4)	16 (4.8)	1 (0.7)
Chronic throat clearing	8 (2.2)	1 (0.7)	6 (1.8)	1 (0.7)
Throat irritation	147 (40.7)	22 (15.6)	132 (39.8)	27 (18.2)
Throat tightness	65 (18.0)	6 (4.3)	33 (9.9)	2 (1.4)
Upper-airway cough syndrome	9 (2.5)	1 (0.7)	3 (0.9)	0
Exercise-induced asthma	2 (0.6)	1 (0.7)	0	0
Maintenance	--	--	--	--
Total Subjects in population	156	61	154	57
Asthma	19 (12.2)	6 (9.8)	1 (0.6)	1 (1.8)
Cough	30 (19.2)	11 (18.0)	31 (20.1)	11 (19.3)
Wheezing	13 (8.3)	6 (9.8)	6 (3.9)	4 (7.0)
Dyspnea	12 (7.7)	1 (1.6)	5 (3.2)	0
Dysphonia	5 (3.2)	1 (1.6)	3 (1.9)	0
Chronic throat clearing	1 (0.6)	1 (1.6)	0	1 (1.8)
Throat irritation	21 (13.5)	5 (8.2)	22 (14.3)	6 (10.5)
Throat tightness	10 (6.4)	0	10 (6.5)	0
Upper-airway cough syndrome	0	0	2 (1.3)	0
Exercise-induced asthma	0	0	0	0

Adapted from 125696/0 Clinical Summary of Safety Table 14.3.1.2.27 and Table 14.3.1.2.29

<u>Clinical Reviewer comment</u>: While the studies were not powered to detect differences in these subpopulations, rates of AEs between treatment and placebo recipients did not demonstrate a clear discrepancy in non-asthmatics and asthmatics. However, a clinical history of asthma may increase the number of moderate systemic allergic reactions and epinephrine use in those taking Palforzia during the up-dosing period (data not shown). As stated above, ACT was administered throughout the studies in the integrated safety database and no concerning change in subjects' asthma control was noted in subgroups 4 to 11 years of age or 12 to 17 years of age, suggesting that although subjects with asthma reported increased occurrence of some respiratory-related adverse events, these events did not affect overall asthma control. These data suggest that the presence of co-morbid conditions at baseline, including other atopic conditions, cannot be used to identify patients at particular increased risk of AEs.

8.5.5 Product-Product Interactions

The study treatment was not evaluated in combination with other oral, epicutaneous, sublingual or subcutaneous immunotherapy products.

Prohibited medications in the main efficacy study, ARC003, included beta blockers. Persons who take beta blockers may be at higher risk for complications from a systemic adverse reaction to the product because they may be unresponsive to epinephrine or inhaled bronchodilators used in the treatment of serious allergic reactions.

8.5.6 Human Carcinogenicity

Not applicable.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Symptoms of overdose of Palforzia in peanut allergic patients may include local and systemic allergic reactions that may be severe or life-threatening.

Clinical reviewer comment: In the clinical studies, study treatments were dispensed in a controlled setting to decrease the chance of subjects ingesting a higher dose than tolerated under clinical observation. In ARC003, the first dose at each new dose level was administered under the direct supervision of a credentialed healthcare provider and the oversight of a physician. This dose, intended for in-clinic administration, was removed from the dosing kit for the assigned dose level. Once a dose was removed from a dosing kit, the kit was dispensed to the subject or held at the site for documented destruction or return to the sponsor's designee (as instructed); dosing kits once opened could not be used for any other dosing interval or any other subject. At each clinic visit, subjects received a kit of capsules to be taken at home according to their specific dose level.

8.5.8 Immunogenicity

Not applicable.

8.5.9 Person-to-Person Transmission, Shedding
Not applicable.

8.6 Safety Conclusions

Pooled safety analysis of 4 clinical studies submitted to the BLA revealed a similar safety profile to that seen in the major efficacy study, ARC003. Treatment with Palforzia resulted in an increased risk of systemic allergic reactions, some of which resulted in increased epinephrine use as a rescue medication compared to placebo recipients. A substantial proportion of subjects treated with Palforzia discontinued due to adverse events, with additional subjects withdrawing due to withdrawal of informed consent and other reasons. In addition, all reports of EoE were seen in Palforzia treated subjects compared to no such cases in placebo recipients. No deaths resulted from Palforzia treatment.

Clinical Reviewer comment: Palforzia use resulted in an increased risk of anaphylaxis in peanut allergic patients compared to avoidance alone in its clinical development

program. Due to the seriousness of this risk, a risk evaluation and mitigation strategy (REMS) with ETASU is recommended to support the licensure of this product to mitigate the risks of systemic allergic reactions associated with Palforzia. The REMS follows the risk mitigation strategies used in the clinical studies submitted to the BLA. Readers are referred to Section 11 of this review for additional information.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No human data is available to establish the presence or absence of the risks due to Palforzia in pregnant women, however, anaphylaxis can cause a dangerous decrease in blood pressure, which could result in compromised placental perfusion and significant risk to a fetus. A pregnancy registry will be conducted as a PMC.

Clinical Reviewer comment: Practice parameters for administration of allergen immunotherapy (AIT) state "allergen immunotherapy can be continued but usually is not initiated in the pregnant patient" and discontinuation of immunotherapy should be considered if the pregnancy occurs during the build-up phase and the patient is receiving a dose unlikely to be therapeutic" [15]. This advice is based on of the risk of systemic reactions and the possible affect to the mother and/or fetus. The PI appropriately states these risks; however, further safety data in pregnant women will be collected via a pregnancy registry PMC. Labeling negotiations are on-going at the time of this review.

9.1.2 Use During Lactation

The safety of Palforzia in women who are lactating has not been established.

Clinical reviewer comment: Lactating women were excluded from the study programs and no subjects became pregnant in the clinical development program. Therefore, the clinical program lacks safety data in lactating women. However, early ingestion of peanut protein is now recognized as an important factor in decreasing the incidence of IgE-mediated peanut allergy [19] and routine avoidance of peanut during infancy is not recommended. Exposure to peanut protein through breast milk in an infant at risk of peanut allergy may be beneficial.

9.1.3 Pediatric Use and PREA Considerations

The applicant seeks an indication for use of Palforzia in individuals 4 through 17 years of age. The applicant is requesting a deferral from PREA requirements for children 1 to < 4 years of age. Following the agreed pediatric study plan, a study to characterize the safety and effectiveness of Palforzia in subjects 1 to < 4 years of age is currently ongoing. The applicant has requested a partial waiver from PREA requirements for subjects < 1 year of age as necessary studies are impossible or highly impracticable because peanut allergy is not typically diagnosed before the age of 1 year.

Clinical Reviewer comment: The applicant requested a partial waiver for subjects <1 year of age on the basis that studies are impossible or high impracticable due to small

numbers of subjects this age with a diagnosis of peanut allergy. The basis for excluding the enrollment of the youngest children in the current development program, was to obtain safety and logistical data in an older population of children prior to evaluating Palforzia in children 1 to <4 years of age. An efficacy and safety study in the younger population has been initiated. This plan follows the agreed Pediatric Study Plan (PSP). The PSP was discussed with the Pediatric Review Committee (PeRC) who agreed with this plan. This reviewer also agrees with the rationale and requests for the partial waiver and partial deferral.

9.1.4 Immunocompromised Patients

The pre-licensure clinical studies that evaluated Palforzia excluded individuals on immunomodulatory medications. Therefore, no data are available on the safety or effectiveness of Palforzia in this population.

9.1.5 Geriatric Use

No studies in the clinical development program included individuals ≥ 65 years of age. The applicant does not seek an indication for use in this age group.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not applicable.

10. CONCLUSIONS

Safety and efficacy data from study ARC003 and safety data derived from studies, ARC004, ARC007, and ARC011 included in the integrated summary of safety (see Section 8) support the safety and effectiveness of Palforzia in individuals 4 through 17 years of age, though with a requirement for a Risk Evaluation and Mitigation Strategy (REMS) to ensure a favorable benefit-risk balance (see below).

The pre-specified primary endpoint success criterion was met in the major efficacy study, ARC003 (Table 5), demonstrating that Palforzia treatment increases the amount of peanut protein tolerated with no more than mild symptom during an oral food challenge. This is important from the perspective that all subjects who entered ARC003 were required to demonstrate objective sensitivity during an entry DBPCFC to a small amount of peanut protein (≤100mg) to be eligible for ARC003 enrollment. This endpoint reflects a clinically meaningful improvement in the ability of a subject to demonstratively tolerate exposure to small amounts of peanut protein that may be present as hidden contaminants in foodstuffs. This endpoint was discussed and endorsed during a public advisory committee (see Section 2.5).

Review of the safety data resulted in a number of concerns associated with Palforzia. These concerns are an increased amount of systemic allergic reactions, epinephrine use, and cases of EoE in Palforzia-treated subjects. While systemic allergic reactions occur throughout the studies at all periods (initial dose escalation, up-dosing, and maintenance), about a quarter of reactions reported during up-dosing (Table 29) occurred at the study site, suggesting subjects are at higher risk for reactions when

administered each new dose in the up-dosing schema. While some systemic allergic reactions are expected when peanut allergic individuals are exposed to peanut protein, this reviewer believes additional risk mitigation measures are necessary to ensure the benefits of this product outweigh the risks in light of the number of systemic allergic reactions and allergic reactions requiring epinephrine administration that occur with Palforzia treatment. To help mitigate the risk of systemic allergic reactions this reviewer specifically recommends a REMS with elements to assure safe use (ETASU) to support licensure. The intent of the REMS is to ensure that individuals undergoing treatment with Palforzia have access to medications to treat systemic allergic reactions and understand that peanut-containing foods must be continuously avoided despite use of this product, and to ensure physicians understand that patients should be observed during the first dose of each up-dosing level in a facility capable of treating allergic reactions. With these risk mitigation strategies in place, the overall benefit-risk profile of Palforzia is acceptable for approval.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 32 below summarizes the risk-benefit considerations for approval of Palforzia.

Table 32: Summary of Risk-Benefit Analysis for Palforzia

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• IgE-mediated peanut allergy is a common disease affecting 5.1% of children 0 to 17 years of age in the US [10]. • Exposure to peanut allergens in allergic individuals can result in systemic allergic reactions that can be life-threatening. • Peanut allergy results in significant impairment of quality of life due to the fear of accidental ingestion as well as the burden of avoiding allergenic foods.	• IgE-mediated peanut allergy is a life-threatening disease that results in significant disruption of quality of life for individuals and their families.
Unmet Medical Need	• No preventative treatment for IgE-mediated allergic reactions including anaphylaxis upon accidental exposure to peanut in peanut allergic individuals exists. • Peanut-allergic individuals must maintain a strict avoidance diet. • When accidental peanut exposures occur, treatment is limited to mitigating the symptoms of allergic reactions either with immediate injection of epinephrine or with antihistamines for milder symptoms.	• In children 4 through 17 years of age, there is an unmet medical need for treatment of IgE-mediated peanut allergy.
Clinical Benefit	• Phase 3 study ARC003 was a double-blind, randomized, placebo-controlled efficacy and safety study that demonstrated the effectiveness of Palforzia in individuals 4 through 17 years of age with the treatment difference (efficacy) estimate of 63.2% (95% CI: 53.0, 73.3). • Study ARC003 met pre-specified key secondary endpoints at the exit DBPCFC at doses of 300mg (68.5% (95%CI: 58.6, 78.5)) and 1000mg (47.8% (95% CI: 38.0, 57.7)) demonstrating a dose-response to Palforzia treatment. • The overall severity of symptoms decreased in ARC003 during the exit DBPCFC in Palforzia recipients compared to placebo recipients, meeting the 3rd pre-specified key secondary endpoint.	• Treatment with Palforzia reduces the severity of allergic symptoms upon exposure to a quantifiable amount of peanut protein during an oral food challenge.
Risk	• Palforzia recipients demonstrate an increase in systemic allergic reactions (in ARC003, 14.2% of Palforzia recipients vs. 3% of placebo recipients), epinephrine use (in ARC003, 14.0% of Palforzia recipients vs. 6.5% of placebo recipients), and allergic symptoms, particularly GI-related allergic symptoms. • Palforzia recipients discontinued at a higher rate than placebo recipients • Twelve cases of EoE in Palforzia recipients were reported in the clinical development program while no placebo recipient developed EoE. • No deaths were associated with Palforzia.	• The evidence indicates that Palforzia use is associated with an increased risk of systemic allergic reactions, allergic reactions requiring epinephrine, and EoE.
Risk Management	• A risk evaluation and mitigation strategy (REMS) program could ensure patients have access to epinephrine, continue to avoid peanut in the diet, and are observed in a clinical setting capable to treating systemic allergic reactions when exposed to a higher dose during up-dosing. • Product labeling could warn patients about the risks of systemic allergic reactions, GI-related allergic reactions, and EoE and to directly to contact a health care professional if any of these signs or symptoms occur.	• To satisfactorily mitigate the risk of systemic allergic reactions this reviewer recommends a REMS with ETASU is required for licensure. • The package insert is adequate to communicate the risks of EoE and GI-related symptoms

11.2 Risk-Benefit Summary and Assessment

IgE-mediated peanut allergy is an increasingly common life-threatening food allergy in children. This condition affects quality of life of individuals and their families due to fear of accidental ingestion and the burden of avoiding allergenic foods, some of which are present as undeclared allergens or food contaminates. Labeling for allergen foods is often confusing for consumers and inadequate to convey allergen content in commercially produced foodstuffs [18]. Therefore, a treatment to diminish the sensitivity of peanut allergic individuals upon accidental exposure to peanut protein is needed.

Data submitted to the BLA establish a benefit of Palforzia as an oral immunotherapy treatment to mitigate allergic reactions, including anaphylaxis, after accidental exposure to peanut in patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy. Major efficacy study ARC003 demonstrated a treatment effect upon exposure to peanut protein in the exit DBPCFC after 12 months of daily treatment. Additionally, during the APAC open public hearing, both patients and caregivers expressed that Palforzia provided meaningful quality of life benefits despite the increased risk of anaphylaxis. Speakers specifically mentioned that the timing of the reactions were perceived to be more predictable and that the daily ingestion of peanut with no to limited symptoms reduced anxiety caused by the unpredictability of reactions with avoidance measures alone. The durability of protection from accidental exposure after discontinuing Palforzia has not been studied. At this time, potentially life-long treatment with Palforzia is anticipated.

Review of safety data submitted to the BLA in controlled and uncontrolled follow-on studies indicates that risks of Palforzia treatment include systemic allergic reactions, allergic symptoms with a preponderance of GI-associated symptoms, and cases of EoE, some of which led to discontinuation of treatment. Some level of allergic symptoms are anticipated based on the nature of the treatment approach, which is exposing individuals with IgE-mediated peanut allergy to peanut proteins contained in Palforzia in an effort to decrease immunologic hyperresponsiveness upon accidental exposure to peanut proteins in routine daily life. However, the complete mechanisms of peanut oral immunotherapy are poorly understood.

The risk of gastrointestinal symptoms caused by Palforzia should be self-evident to caregivers and patients who can determine if the benefits of the product outweigh this risk of intolerance. However, Palforzia use is associated with an increase in the number of systemic allergic reactions, including those that resulted in administration of epinephrine by both study staff in the clinic and by subjects at home. Additionally, while most systemic allergic reactions occurred within 2 hours of Palforzia administration, there were reports of reactions without concomitant accidental food exposure that occurred outside of this time frame. These incidents support the continued need for direct access to auto-injectable epinephrine at all times regardless of Palforzia therapy. Given the frequency of systemic reactions in Palforzia recipients compared to placebo recipients who practiced peanut avoidance alone, this reviewer recommends additional risk mitigation measures to support licensure of Palforzia and to ensure a favorable benefit-risk balance. Specifically, this reviewer recommends additional measures outside of the USPI and routine pharmacovigilance to ensure patients understand the limitations

of the benefits and risks associated with Palforzia use. The risk mitigation measures built into the clinical protocols should be carried forward into clinical practice. These measures include the need for epinephrine access at all times and for continued dietary peanut avoidance. Additionally, the first dose of all dose escalations should occur in a health setting to ensure patients are able to tolerate the escalated dose before self-administration at home. The safety data from this program and the recommendation for additional risk mitigation measures to be formalized under a REMS were presented to the APAC who affirmed this recommendation by voting 8 to 1 affirmatively that the available safety data, in conjunction with additional safeguards, was adequate to support the use of Palforzia in patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy.

Given the clinical benefit observed in major efficacy study ARC003, the overall risk-benefit assessment is favorable within the parameters of a REMS with elements to ensure safe use (ETASU) program to mitigate the risk of systemic allergic reactions. The REMS with ETASU are discussed in additional detail in the REMS memorandum.

11.3 Discussion of Regulatory Options

The approval of Palforzia was based on efficacy and safety data from one major study, ARC003, and safety data from 3 additional studies (ARC004, ARC007, and ARC011). The small number of adult participants in study ARC003 (N=55) precluded a reasonable assessment of efficacy and safety in adult subjects. Therefore, this reviewer concurs with Aimmune's proposal to exclude adults from the indication. A study in children 1 to <4 years is on-going and is intended to provide efficacy and safety data in young children post-approval. This reviewer concurs with Aimmune's request for a partial waiver in children < 1 year of age.

The safety profile of Palforzia, as documented in this review, requires additional risk mitigation to ensure the benefits of the product outweigh the risks. As such, this reviewer recommends a REMS with ETASU to support the licensure of Palforzia. In clinical studies the potential for anaphylaxis with Palforzia administration was anticipated based on the mechanism of action of oral immunotherapy desensitization procedures (i.e., the act of giving a peanut allergic patient small doses of peanut). In the clinical trials, the risks of Palforzia were mitigated by elements incorporated in the study procedures. All dose escalations were performed under direct observation and medical supervision at clinical sites. Study participants and caregivers were provided auto-injectable epinephrine, trained in its use, and instructed to remain on a peanut-free diet. The goal of any allergen desensitization procedure, and in particular one self-dosed by a patient, would be to achieve a dosing procedure where product-related anaphylaxis does not occur while achieving protection from accidental exposures. As outlined throughout the safety review, anaphylaxis and Palforzia-related epinephrine use was seen during all stages of Palforzia dosing but particularly during the up-dosing procedures. The risk mitigation elements incorporated into the clinical program are reflected in the Palforzia REMS with ETASU program. In addition, the PI and medication guide will discuss these risks and include risk mitigation strategies for systemic allergic reactions and GI symptoms that may indicate EoE.

11.4 Recommendations on Regulatory Actions

Palforzia is recommended for approval (21 CFR 601.4) based on the data from the primary efficacy endpoint of study ARC003 in children 4 through 17 years of age as oral immunotherapy treatment to mitigate allergic reactions, including anaphylaxis, after accidental exposure to peanut.

11.5 Labeling Review and Recommendations

Labeling negotiations remain ongoing at the time of this review.

11.6 Recommendations on Postmarketing Actions

A study in children 1 to <4 years of age is on-going as a deferred pediatric study to address PREA. No additional postmarketing studies to further characterize safety are planned because the safety data submitted to the BLA are sufficient to characterize the type and frequency of adverse events associated with Palforzia. This reviewer recommends that the pregnancy registry proposed by Aimmune in its application be outlined as postmarketing commitment.

The applicant submitted a REMS with ETASU after discussion and agreement with the review team including OBE and CDER DRISK. The focus of the REMS with ETASU is site preparation of healthcare facilities, prescriber education and patient education and patient attestation that includes an agreement to ensure access to epinephrine and avoid dietary peanut. The PI and medication guide are not part of the REMS but have been reviewed to convey these risks to healthcare providers and patients, respectively. Postmarketing audits to support the REMS program will be conducted. Readers are referred to the CDER DRISK consult and the REMS memorandum for additional details.